A clinical and neurocognitive study of recurrent depression and bipolar spectrum disorder in young adults

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Declaration

I declare that this thesis is my own work and that it has not been submitted elsewhere as part of another diploma, degree or professional qualification.

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21ST JULY 2005

Date

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Abbreviations

AAO	Age At Onset
ANOVA	Analysis of Variance
AUDIT	Alcohol Use Disorders Identification Test
BDNF	Brain Derived Neurotrophic Factor
BPAD	Bipolar Affective Disorder
BSAT	Brixton Spatial Anticipation Test
BSD	Bipolar Spectrum Disorder
CBT	Cognitive and Behavioural Therapy
CGI	Clinical Global Impression
CPT	Continuous Performance Test
CVLT	California Verbal Learning Test
DAST-20	Drug Abuse Screening Test
DSM-IV	Diagnostic and Statistical Manual, fourth edition
DSST	Digit Symbol Substitution Test
FIGS	Family Interview for Genetic Studies
GAF	Global Assessment of Functioning
HRSD	Hamilton Rating Scale for Depression
HPA axis	Hypothalamic Pituitary Adrenal axis
ICD-10	International Classification of Diseases, 10
MANOVA	Mutivariate Analysis of Variance
MDD	Major Depressive Disorder
NART	National Adult Reading Test
SCID-1	Structured Diagnostic Interview for DSM-IV, version 1
SPSS	Statistical Package for Social Sciences
SSRI	Selective Serotonin Reuptake Inhibitor
TMT-A	Trail-making Test, part A
TMT-B	Trail-making Test, part B
WAIS-R	Weschler Adult Intelligence Scale, revised
WCST	Wisconsin Card Sort Test
WHO	World Health Organisation

Abstract

The presentation and neurobiology of depression in young adults is an important but under-studied area of psychiatric research. Many young adults with early-onset recurrent major depressive disorder (MDD) have a strong genetic loading for mood disorder and, in the longer term, may be at high risk of developing bipolar affective disorder (BPAD). The objectives of this thesis were two-fold: firstly, to assess the prevalence and clinical validity of bipolar spectrum disorder (BSD) in a consecutive sample of young adults with recurrent depression; and secondly, to carry out a neurocognitive study comparing clinically recovered (euthymic) young adults with recurrent MDD, euthymic BSD patients and well-matched controls. Eighty-seven young adults presenting with recurrent depression were recruited from consecutive referrals to a psychiatric clinic at a University Health Service. Of these, 14 had BPAD, 27 had BSD and 46 had recurrent MDD. The classic criteria used to assess the validity of psychiatric diagnoses (namely, clinical phenomenology, clinical course, family history and treatment response) were applied to the BSD group of patients. This provided only modest support for the validity of the BSD criteria according to clinical parameters. However, on neurocognitive testing, there were significant differences between BSD patients, MDD patients and controls in terms of performance on tests of attention, executive function and declarative memory. This finding suggested that the diagnsotic criteria for BSD were able to identify a sub-group of young adults with recurrent depression and strong bipolar features (such as a family history of bipolar disorder or a personal history of antidepressant-associated hypomania) who performed less well than young adults with more straightforward unipolar depression on tests of prefrontal and hippocampal functioning. The implications of these findings for the concept of bipolar spectrum disorder, and for our understanding of the neuropsychology of mood disorders, are discussed. Limitations of this work and directions for future research are also considered.

Chapter 1 Introduction

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1.1 Depression in young adults

Using the measure of disability-adjusted life years, the Global Burden of Disease report determined that in 1990 unipolar major depression was the fourth leading cause of disease burden in the world [1]. By 2020, it is estimated that depression will be the second leading cause of disease burden worldwide [2]. Research efforts investigating the causes and treatment of depression represent a major challenge for psychiatry and are likely to have considerable implications for public health [3].

The term 'depression' can be understood to describe a heterogeneous collection of disorders, ranging from mild subthreshold forms such as dysthymia through to major depressive disorder (MDD) and more severe forms such as bipolar affective disorder (BPAD). Depressive subtypes can differ in terms of factors such as age at presentation, gender and psychiatric or medical comorbidity. To date, depressive disorders with an onset in adolescence or early adulthood have been a relatively neglected area of mood disorder research. This is despite evidence to suggest that severe and chronic forms of mood disorder often begin early in life.

1.1.1 Epidemiology of depression in young adults

Although most epidemiological studies estimate that at least 5% of men and 10% of women will suffer from depression at some point during their lifetime [4, 5], there is a relative paucity of studies focusing on populations of adolescents and young adults. Depressive symptoms appear to be relatively common in early adulthood. A recent Finnish study of young adults identified a one-month prevalence for major depression of 10% [6]. It also appears to be the case that adolescents with sub-diagnostic levels of depressive symptoms will have higher subsequent rates of adulthood depression [7]. When symptom severity reaches the threshold for diagnosis in adolescence it is likely that this depression will recur during adult life [8, 9].

The Maudsley long-term follow-up study of child and adolescent depression, which followed 149 subjects over 20 years, found that 62.4% experienced a recurrence of major depression [10]. Rates of suicidal behaviour were also high, with 44.3% attempting suicide at least once during the follow up period [11].

That women are twice as likely as men to suffer from depression is a consistent finding in psychiatric epidemiology and does not appear to be simply a consequence of females being more likely to report, recall or seek help for depressive symptoms. Before puberty, boys are slightly more likely than girls to experience depression but between the ages of 11 and 13 this trend is reversed, with girls outnumbering boys by two to one [12]. This predominance of females over males then persists for the next 35 to 40 years, although the reasons for this are largely unknown. Pubertal changes in gonadal steroids may be part of the explanation. It has been suggested that hormonal changes in adolescence, combined with dramatic changes in social environment, role expectancies and relationships, might stimulate

the development of greater affiliative needs in females, such as a preference for intimacy and emotional responsiveness. One possible result of this is that adolescent girls may be more vulnerable to the effects of negative life events, especially those events with interpersonal consequences [13].

In the United Kingdom, suicide is now the commonest cause of death in young men between the ages of 25 and 34 [14]. Epidemiological studies suggest that although factors such as poor schooling, poverty and unemployment are important, the strongest risk factors for suicide in this group are a personal history of mental illness, and a family history of suicide or mental illness [15]. In a psychological autopsy study of suicide in 27 young people aged between 15 and 24, Houston and colleagues found that 70.4% suffered from a mental illness and that depression was the most common diagnosis, affecting 55.6% of those studied [16]. Almost 30% of these subjects had a diagnosis of personality disorder and one third had another co-morbid psychiatric disorder.

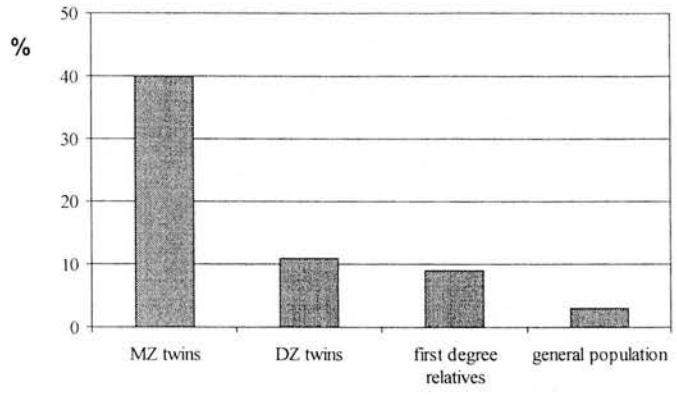
1.1.2 Aetiology of depression in young adults

Under a commonly held model, depressive episodes in young adults probably occur as a consequence of a wide range of environmental risk factors interacting with genetic predispositions for mood disorder. A large body of research has established that factors such as a positive family history of mood disorder, childhood adversity, recent life events and drug and alcohol misuse are important in the aetiology and pathogenesis of depression.

The role of genetics

Over the last 50 years a number of family and twin studies have highlighted the importance of genetic predisposition in the development of depressive disorders. The prevalence of depression in the relatives of depressed probands is approximately three times that in the general population [17] and concordance rates for monozygotic and dizygotic twins are approximately 40% and 11% respectively (figure 1) [18, 19]. Adoption studies of monozygotic twins reared apart have suggested that most of the familiality in depression occurs for genetic rather than environmental reasons [20].

Figure 1. Family and twin studies for major depressive disorder



Despite evidence for the genetic transmission of depression, molecular genetic approaches have so far been inconclusive. Although a combination of linkage and association studies have identified a number of candidate genes, such as tyrosine hydroxylase, catechol-O-methyltransferase, the serotonin transporter, and several serotonin receptors (including 5HT2c, 5HT1a and 5HT2a), none of the findings to date have been consistently replicated [21].

One explanation for this is that mood disorders are genetically and phenotypically heterogeneous. Depression probably encompasses several clinical sub-groups, some of which are likely to be more heritable than others. One such sub-group may be recurrent early-onset major depressive disorder (MDD), which has been defined as two or more episodes of major depression with onset before the age of 22 [22, 23]. Recurrent MDD under this definition is associated with a strong family history of affective disorder (over one third of first degree relatives and one fifth of extended relatives have a lifetime history of depression) and appears to follow a

particularly malignant course, with frequent recurrence, poor response to treatment and high psychiatric and physical morbidity [23, 24].

Childhood adversity

Childhood physical, emotional and sexual abuse are established as important risk factors for the development of a range of psychiatric disorders in adult life and are increasingly recognised as important in early-adulthood psychopathology. Traumatic experiences can interfere with normal emotional and psychological development with the result that abused or neglected individuals often struggle to negotiate the maturational tasks of adolescence and early-adulthood [25].

The observation that not all abused individuals develop significant psychopathology in later life suggests that our susceptibility to stress may be dependent upon our genetic make-up. To some degree, this has been demonstrated recently in the Dunedin longitudinal study where it was shown that individuals with the less transcriptionally active short (S) allele of the promoter region of the serotonin transporter gene, in contrast to those with the long (L) allele, were more likely to experience an episode of major depression in the context of life events [26]. This notion of genetic resilience is also supported by recent work on depression in adolescent girls. The Virginia Twin Study of Adolescent Behavioural Development was used to assess the effects of independent life events on depression in 184 female twin pairs [27]. Here it was found that there was no effect of independent life events on depression in the absence of a positive history of emotional disorder in parents, suggesting a gene-environment interaction whereby genetic factors played a significant role in mediating the effects of stress in this group [27].

Recent life events

Although it is established that negative life events can precipitate depression, the association is a complex one and is likely to operate bidirectionally: people with depression are more likely to generate stressful events, and individuals with a higher genetic loading for affective disorder are more likely to experience depression after a stressful event than those with low genetic loading [27, 28].

In recurrent MDD the association between life events and depression is strongest for early episodes and becomes weaker as the number of episodes increases [29]. Recurrent depressive episodes tend to become more autonomous and are progressively less linked to environmental adversity, a phenomenon which has been termed 'kindling' [30]. Kindling tends to be most marked in individuals at low genetic risk of depression with those with at high genetic risk exhibiting 'prekindling'. Prekindled individuals appear to become depressed after only minimal environmental provocation [31]. One important implication of this is the possibility that young people with a strong family history of affective disorder may be constitutionally vulnerable to the effects of even minor psychosocial stressors.

Substance misuse

Drug and alcohol use in adolescence are important risk factors for the development of affective disorders in early adulthood and are likely to complicate the long term course of depression. In a five-year longitudinal study of 155 adolescent females, Rao and colleagues found that 18.7% developed a substance misuse disorder and that substance misuse was a marker for the eventual occurrence of depression [32]. Conversely, when 274 previously depressed adolescents were followed to age 24, two

thirds experienced another depressive episode and, within the remaining third who did not, 77% were found to have a substance misuse disorder [33].

Cannabis use in the United Kingdom has now reached such a high level that the majority of young people have tried it at some point [34]. Although an association between cannabis and psychotic illness (especially schizophrenia) is well recognized, much less attention has been paid to its association with mood disorder. Evidence is emerging for an important relationship between cannabis use and depression in young adults [35]. Although cross-sectional surveys confirm strong correlations between cannabis and depression [36], they tell us little about the causal mechanisms in operation. It may be that those who are pre-morbidly depressed are more likely to use cannabis as a form of self-medication [37]. Alternatively, higher use in depressed groups may be related to confounding factors such as social deprivation, early adjustment problems and poor academic achievement [38].

Two recent longitudinal studies support the view that regular cannabis use at a young age is a precursor of depression in early adulthood. In the first, 1601 students were followed between the ages of 14 and 21 [39]. It was found that daily cannabis use in adolescence was associated with a significant risk of anxiety and depression in early adulthood. This was particularly true for teenage girls: those who used cannabis on a daily basis were 5 times more likely to have depression than non-users [39].

In a similar investigation, the New York State Children in the Community Study, a cohort of 736 children were followed between the ages of 14 and 27 [40]. Here it was found that regular cannabis use was strongly predictive of depression as a young adult. Furthermore, those who began to use cannabis in their early teens were at higher risk than those who began in their early twenties, suggesting that a critical

period might exist during which the brain is particularly sensitive to the neurotoxic effects of cannabis.

There is also considerable co-morbidity between alcohol use and depression in young adults [41]. That alcohol use at a young age is associated with a higher risk of depression in young adulthood is also supported by the New York State Children in the Community Study. Earlier alcohol use significantly predicted not only depression but also any substance use disorder and alcohol dependence by age 27 [40].

1.1.3 Pathophysiology of depression

In recent years the classical monoamine theory of depression, although still relevant, has matured into a molecular and cellular theory, which suggests that overactivity of the hypothalamic-pituitary-adrenal (HPA) axis (cortisol hypersecretion) is central to the pathophysiology of depression [17, 42]. Traditionally, HPA overactivity has been demonstrated in severely depressed patients by non-suppression of morning cortisol in the dexamethansone suppression test (DST). However, this test did not prove to be an abnormality that was specific to mood disorders - dexamethasone non-suppression was subsequently identified in a number of other psychiatric disorders, including schizophrenia and dementia. A more recent modification of the DST, the combined dexamethasone/CRH (corticotrophin releasing hormone) test, has been shown to be more specific to depression [43] and is also exaggerated in the clinically-well first degree relatives of depressed probands [44, 45].

It is uncertain how this hyperactivity of the HPA axis arises. It may be a consequence of severe early life stress. For example, Goodyer and colleagues have found that suboptimal care during the first six months of life is associated with higher morning cortisol in adolescence and higher risk for subsequent psychopathology [46]. HPA activity may also arise from a strong genetic loading for affective disorder [47].

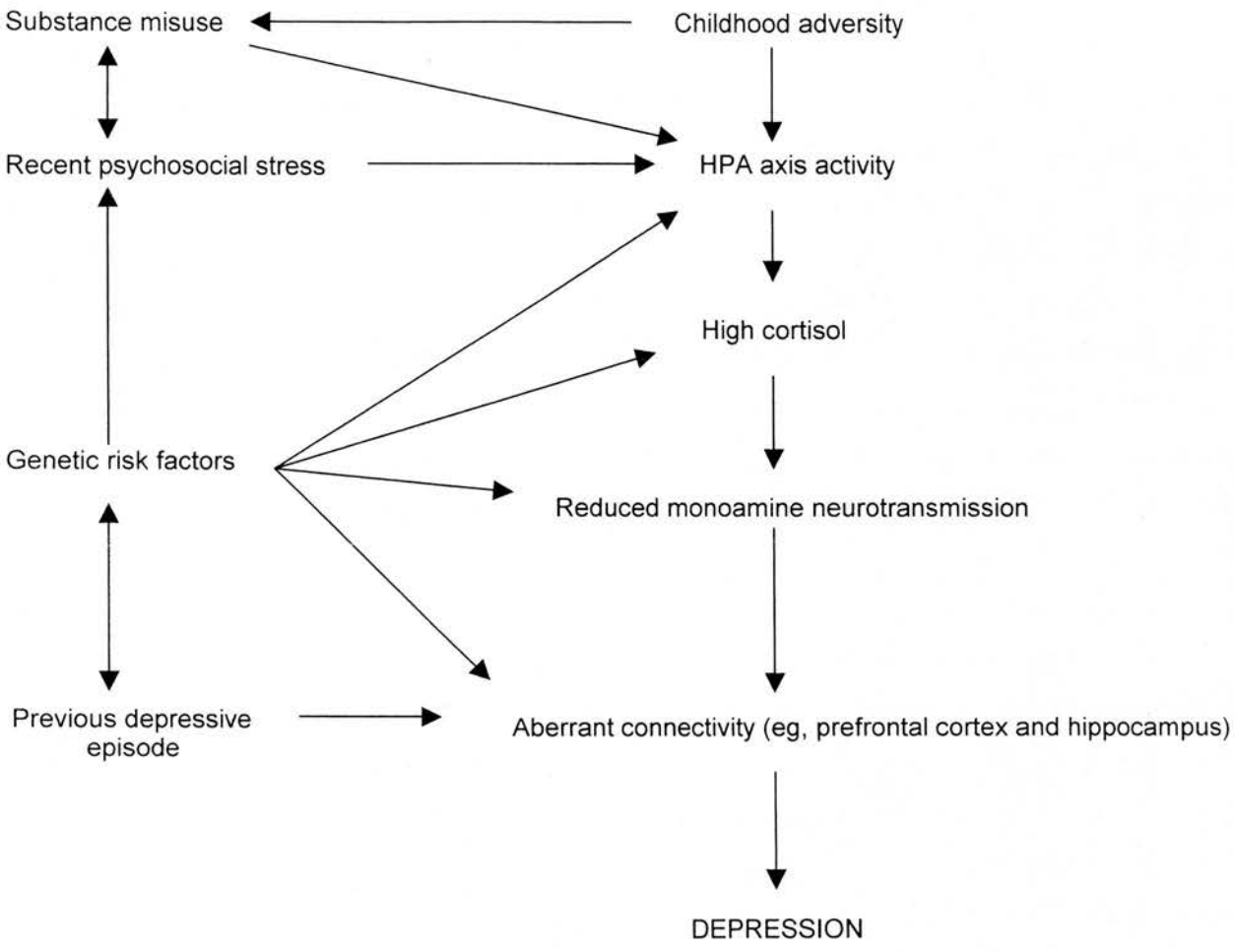
Recent work suggests that high levels of corticosteroids may contribute to dysregulation of the momoamine system [48]. In animal models, cortisol alters the expression of 5HT1a and 5HT2c receptors [49, 50]. In humans, high morning cortisol contributes to downregulation of 5HT1a receptors thereby reducing serotonin neurotransmission and making depressive states more likely [51]. Animal and human studies have also suggested that cortisol may be toxic to hippocampal neurones and

that this toxicity contributes to ongoing HPA dysregulation in depressive disorders [17, 42, 52].

Although magnetic resonance imaging studies have demonstrated reduced hippocampal volume in patients with major depression [53], this may either be a reflection of pre-morbid vulnerability or a consequence of repeated episodes of illness [54]. Furthermore, it should be appreciated that although depressive disorders may sometimes be associated with functional and structural abnormalities in the brain, they probably occur not as a result of an abnormality within one particular region but because of dysfunction within dynamic neural networks such as those connecting the frontal cortex with areas such as the hippocampus, amygdala and thalamus [55, 56]. This area is explored in more detail later in this chapter within a review of the literature of neurocognitive impairment in mood disorders.

The precise relationships between elevated cortisol, aberrant monoamine transmission and depressive neural circuitry remain to be fully worked out. However, on the basis of research to date, a simplified neurobiological model of the pathophysiology of depression can be constructed (figure 2).

Figure 2. Neurobiological model of depression



1.1.4 Clinical presentation of depression in young adults

Depression varies widely in its clinical presentation. In adolescence and young adulthood atypical symptoms are common whereas more classic melancholic presentations appear to be relatively rare [57]. Younger adults with depression also tend to report more irritability and anxiety [58]. When depression has begun early in life and has recurred, it may be that the possibility of an emerging bipolar disorder should be considered. Two case reports which are taken, with permission, from patients participating in the current study are presented below to illustrate the clinical presentation of depression in young adults.

Case report 1 ***'Anxious-hostile' presentation of depression in young adult***

A 21 year-old university student was assessed by a psychiatrist on an orthopaedic ward two days after a violent suicide attempt. He had jumped form a height of 60 metres sustaining a broken leg, multiple cuts, severe bruising and a minor head injury. He had taken the decision to kill himself after two weeks of escalating anxiety, irritability, disturbed sleep and agitation in the lead up to an important set of exams. He denied suffering from low mood, anhedonia, fatigue or changes in his appetite. He had strong obsessional and perfectionistic traits in his personality and had become convinced that, despite studying extremely hard, he was destined to fail his exams and that life was no longer worth living. He had taken the decision to kill himself only a few hours before the suicide attempt. Twelve months previously he had been admitted briefly to a psychiatric ward following an impulsive overdose of antidepressant medication. This previous episode of depression had also been characterised by symptoms of anxiety and irritability rather than more classic

depressive features. After transfer from the orthopaedic ward he made a good recovery as an inpatient on a general psychiatric ward and eventually responded well to venlafaxine at a dose of 225mg per day.

This case is an example of depression in a young man with prominent anxiety, irritability and impulsivity. Although this kind of presentation is well recognised in adolescent populations [58], it does not fit easily into our current adult ICD-10 and DSM-IV diagnostic classifications. Depressions characterised by irritability and hostility may be misinterpreted by clinicians as personality dysfunction and can be associated with dangerous impulsive behaviour and potentially lethal acts of self-harm.

Case report 2 ***Possible bipolar depression in a young adult***

A 20 year-old woman was referred by her GP to the psychiatrist because she described mood swings. She gave a four-month history of feeling depressed and irritable with excessive fatigue, overeating, weight gain and hypersomnia. She was also drinking heavily, on average over 70 units of alcohol per week. She felt that she first had problems with her mood at the age of 12 when she became over-active and disruptive at school, having previously been a reserved and conscientious pupil. Over the years she described several different periods in her life when her mood seemed to switch suddenly between episodes of depression and short-lived periods of euphoria with overactivity and decreased need for sleep. These periods of elevated mood always lasted less than 2 days and tended to give way to longer periods of low mood and irritability. She denied ever having harmed herself but had been admitted to hospital three times as a teenager because of excessive alcohol consumption. She had

a strong family history of affective disorder with both parents and an elder brother suffering from MDD. The impression was that she was currently suffering from an episode of MDD against a background of significant mood instability and longstanding alcohol misuse. There was nothing in her history or presentation to suggest that she had a personality disorder. She was treated with sodium valproate, a mood stabiliser, up to a dose of 800 mg per day and made a good symptomatic recovery within four weeks.

This is a case of depression characterised by excessive fatigue, hyperphagia, weight gain and hypersomnia. This pattern of symptoms is described as 'atypical' depression in DSM-IV and may be more common in bipolar disorder than in recurrent unipolar disorder [59, 60]. Even though this patient does not meet the DSM-IV criteria for bipolar affective disorder, that is, periods of depression alternating with hypomania of at least four days duration, she describes considerable mood instability and appears to have reacted in an adverse way to antidepressants. Recognition of a possible bipolar depression in this case rather than unipolar depression may have important implications for future pharmacological treatment choices, particularly because antidepressants may have the potential to act as mood destabilisers in a proportion of patients with a bipolar disorder by triggering mania, mixed affective states and rapid-cycling. In a recent review of data from published reports and clinical trials, Goldman and Truman estimated that between 25% and 33% of bipolar patients were inherently susceptible to antidepressant-induced manias [61].

1.2 Classification of affective disorders

As with most diagnostic categories in psychiatry, the classification of affective disorders remains a work in progress. At the present time, the two most widely used classifications are the ICD-10 Classification of Mental and Behavioural Disorders published by the World Health Organisation (abbreviated to ICD-10) [62] and the Diagnostic and Statistical Manual, fourth revision, of the American Psychiatric Association (DSM-IV) [63].

1.2.1 Classification of depression and bipolar disorder

Both ICD-10 and DSM-IV are organised as a series of categorical diagnoses. In ICD-10 the major categories of mood disorder are manic episode (F30), bipolar affective disorder (F31), depressive episode (F32), recurrent depressive disorder (F33) and persistent mood disorders (F34).

The criteria for a depressive episode in ICD-10 are outlined in figure 3. For DSM-IV, a major depressive episode (MDE) is diagnosed according to the criteria outlined in figure 4. Both ICD-10 and DSM-IV use a checklist of the same core depressive symptoms: a minimum number of depressive symptoms is required to be present over a two week period. ICD-10 also permits grading of the severity of the depressive episode as mild, moderate or severe depending on the number of depressive symptoms present. In DSM-IV, at least 5 depressive symptoms over the 2 week period are required for the diagnosis of a major depressive episode (MDE). It can be seen that although both systems are essentially categorical, ICD-10 also allows for some dimensional expression of severity.

Figure 3. Depressive episode (ICD-10) [62]

A General criteria (G) for a depressive episode:

- G1 lasts for at least 2 weeks
- G2 no history of hypomanic or manic symptoms
- G3 episode is not attributable to psychoactive substance use or any organicity

B At least two of the following three symptoms must be present:

1. depressed mood that is definitely abnormal for the individual, present for most of the day almost every day, largely uninfluenced by circumstances, and sustained for at least 2 weeks.
2. loss of interest or pleasure in activities that are normally pleasurable.
3. decreased energy or increased fatigability

C Additional symptoms form the following list (mild depressive episode, at least 4 in total; moderate depressive episode, at least 6 in total; severe depressive episode, at least 8 in total).

1. loss of confidence or self-esteem
2. unreasonable feelings of self-reproach or excessive or inappropriate guilt
3. recurrent thoughts of death or suicide, or any suicidal behaviour
4. complaints or evidence of diminished ability to think or concentrate, such as indecisiveness or vacillation
5. change in psychomotor activity, with agitation or retardation (either subjective or objective)
6. sleep disturbance of any type
7. change in appetite (decrease or increase) with corresponding weight change

D A fifth character may be used to specify the presence or absence of the 'somatic syndrome' which is defined as at least 4 of the following symptoms:

1. marked loss of interest in activities that are normally pleasurable
2. lack of emotional reactions to events or activites that normally produce an emotional response
3. waking in the morning 2 hours or more before the usual time
4. depression worse in the morning
5. objective evidence of marked psychomotor retardation or agitation (remarked on or reported by other people)
6. marked loss of appetite
7. weight loss (5% or more of body weight in the past month)
8. marked loss of libido

Figure 4. Major Depressive Episode (DSM-IV) [63]

In the same 2 weeks, the patient has had 5 or more of the following symptoms, which are a definite change from usual functioning. Either depressed mood or decreased interest or pleasure must be one of the five.

1. Mood. For most of nearly every day, the patient reports depressed mood or appears depressed to others.
2. Interests. For most of nearly every day, interest or pleasure is markedly decreased in nearly all activities (noted by the patient or by others).
3. Eating and weight. Although not dieting, there is a marked loss or gain of weight (such as five percent in one month) or appetite is markedly decreased or increased nearly every day.
4. Sleep. Nearly every day the patient sleeps excessively or not enough.
5. Motor activity. Nearly every day others can see that the patient's activity is agitated or retarded.
6. Fatigue. Nearly every day there is fatigue or loss of energy.
7. Self-worth. Nearly every day the patient feels worthless or inappropriately guilty. These feelings are not just about being sick; they may be delusional.
8. Concentration. Noted by the patient or by others, nearly every day the patient is indecisive or has trouble thinking or concentrating.
9. Death. The patient has had repeated thoughts about death (other than the fear of dying), suicide (with or without a plan) or has made a suicide attempt.

Notes:

- These symptoms cause clinically important distress or impair work, social or personal functioning.
- They don't fulfil DSM-IV criteria for Mixed Episode.
- This disorder is not directly caused by a general medical condition or the use of substances, including prescription medications.
- Unless the symptoms are severe (defined as severely impaired functioning, severe preoccupation with worthlessness, ideas of suicide, delusions or hallucinations or psychomotor retardation), the episode has not begun within two months of the loss of a loved one.

ICD-10 and DSM-IV differ more substantially from each other in terms of the diagnostic criteria for bipolar affective disorder (BPAD). The major categories of BPAD in ICD-10 are: current episode hypomanic (F31.0); current episode manic with (F31.2) or without (F31.1) psychotic symptoms; current episode mild or moderate depression (F31.3); current episode severe depression with (F31.5) or without (F31.4) psychotic symptoms; current episode mixed (F31.6); currently in remission (F31.7); and 'other' bipolar disorders (F31.8). As with the approach to diagnosing depression, ICD-10 uses a checklist of hypomanic symptoms and permits grading of the severity of both the hypomanic/manic episodes and the depressive episodes as mild, moderate or severe and with or without the somatic syndrome or psychotic symptoms.

Figure 5. Core manic symptoms in ICD-10 and DSM-IV

Manic symptom	***DSM-IV***	***ICD-10***
Elevated mood	+	+
Irritable mood	+	+
Increased self esteem or grandiosity	+	+
Decreased need for sleep	+	+
Increased talkativeness	+	+
Flight of ideas	+	+
Distractibility	+	+
Increased social activity or contacts	+	+
Psychomotor agitation	+	+
Risk-taking behaviour	+	+
Increased sexual activities		+

As outlined in figure 5, both ICD-10 and DSM-IV use essentially the same checklist of core manic symptoms to diagnose hypomania and mania ('increased sexual activities' is included in DSM-IV within the category of 'increased risk taking behaviour').

In ICD-10, hypomania is considered to be a lesser degree of mania lasting 'several days' and causing 'considerable interference with work or social activity'. By contrast, DSM-IV stipulates that hypomania occurs '*without* marked social or occupational dysfunction' (leading to a diagnosis of bipolar II disorder, figure 6). Full mania in DSM-IV refers to any persistent elevation of mood lasting more than a week that causes functional impairment (bipolar I disorder, figure 7). These subtle differences between the two classifications mean that many patients who under ICD-10 would be considered to have hypomania (that is, having hypomanic symptoms that cause interference with work or social activity) would actually be excluded from a DSM-IV diagnosis of hypomania because of this functional impairment and would be considered to have DSM-IV mania.

Figure 6. DSM-IV criteria for a hypomanic episode

A) A distinct period of persistently elevated, expansive or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual nondepressed mood.

B) During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

1) inflated self-esteem or grandiosity

2) decreased need for sleep (e.g., feels rested after only 3 hours of sleep)

3) more talkative than usual or pressure to keep talking

4) flight of ideas or subjective experience that thoughts are racing

5) distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)

6) increase in goal-directed activity (at work, at school, or sexually) or psychomotor agitation

7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C) The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic.

D) The disturbance in mood and the change in functioning are observable by others.

E) The mood disturbance not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features.

F) The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication or other treatment) or a general medical condition (e.g., hyperthyroidism)

Note: Hypomanic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar II disorder.

Figure 7. DSM-IV criteria for a manic episode

A) A distinct period of abnormally and persistently elevated, expansive or irritable mood, lasting at least 1 week (or any duration if hospitalisation is necessary)

B) During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

1) inflated self-esteem or grandiosity

2) decreased need for sleep (e.g., feels rested after only 3 hours of sleep)

3) more talkative than usual or pressure to keep talking

4) flight of ideas or subjective experience that thoughts are racing

5) distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)

6) increase in goal-directed activity (at work, at school, or sexually) or psychomotor agitation

7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C) The symptoms do not meet criteria for a Mixed Episode

D) The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

E) The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication or other treatment) or a general medical condition (e.g., hyperthyroidism)

Note: Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar I disorder.

1.2.2 The bipolar spectrum concept

In recent years there has been renewed interest in the concept of a mood disorder spectrum. It has been suggested that diagnostic systems such as DSM-IV fail to detect a significant proportion of recurrently depressed patients with mild bipolar features who may be more usefully considered to have a 'soft bipolar' or 'bipolar spectrum' disorder. It is also the case that failure to recognise early bipolar disorders can delay treatment and worsen prognosis. Although this debate was started over 20 years ago by authors such as Akiskal, it has gathered momentum in recent years because of longitudinal follow up studies and re-evaluations of existing epidemiological data. This controversial area of nosology also has an important historical dimension.

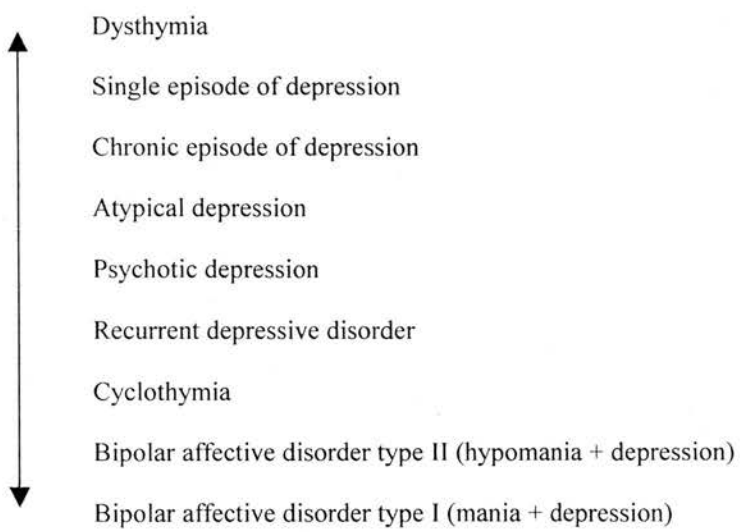
Historical considerations

Emil Kraepelin created a broad view of manic-depressive insanity which encompassed not only less severe, attenuated forms but also most of the domain of major depressive disorders [64]. Several important studies in the second half of the last century divided this unitary model of affective disorders into unipolar and bipolar disorders. In the 1950s, Leonard observed from his cohort of patients with recurrent depression that those who also had a history of mania tended to report more mania in their families than patients who only suffered from depressive episodes [65]. In the 1960s Angst [66] and Perris [67] provided independent family history data to support this. Several lines of evidence subsequently supported the validity of a unipolar-bipolar division: twice as many women as men appeared to suffer from unipolar depression whereas the ratio in bipolar disorder was 1:1; bipolar subjects tended to

have an earlier age of onset; and mortality (mostly through suicide) was consistently higher in the bipolar group [68]. This dichotomous conceptualisation of unipolar versus bipolar disorder is reflected today in the ICD-10 and DSM-IV definitions discussed above.

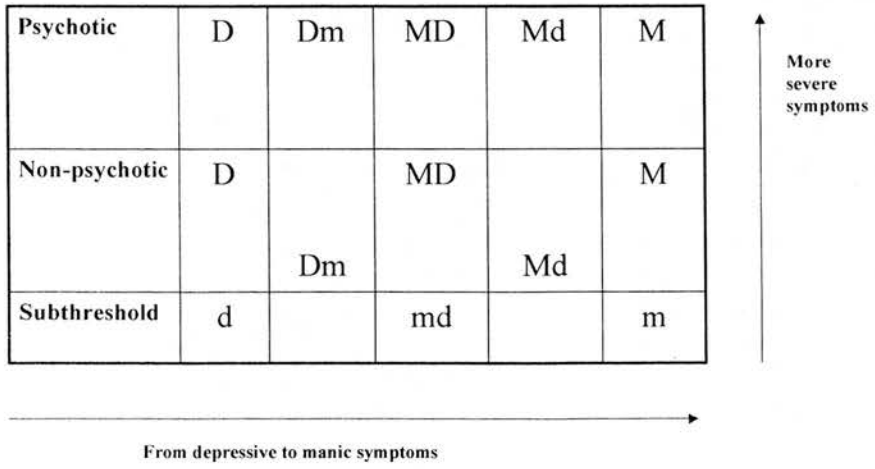
Although ICD-10 and DSM-IV have undoubtedly been of considerable value in clinical practice and research, it may also be the case that they fail to capture the complexity of many psychiatric presentations. By virtue of their multifactorial aetiology, most psychiatric disorders tend to present clinically along a dimension, or spectrum, of severity. For mood disorders, one of the consequences of this has been the proliferation of a large collection of diagnoses. It has been suggested that patients with mood disorders are better conceptualised as lying somewhere on a spectrum of severity ranging from dysthymia at one end to full-blown manic-depressive psychosis at the other (figure 8) [68]. Under this kind of model, classic manic-depression (bipolar I in DSM-IV) would be a relatively infrequent presentation of the broad clinical spectrum of affective illness.

Figure 8. The affective spectrum [68]



In a similar proposal for the bipolar spectrum, Angst and Gamma have suggested a diagnostic model that shows a continuum from purely depressive to purely manic symptoms along a horizontal plane and a gradient of symptom severity along a vertical plane (figure 9) [69]. Three subtypes of bipolar I disorder are recognised: pure mania (M); predominant mania with mild depression (Md); and severe mania with severe depression (MD). Between the purely depressive disorders and the bipolar I subtypes lies bipolar II disorder, characterised by major depressive episodes with hypomania (Dm). This spectrum concept does not reject the DSM-IV or ICD-10 categories, but provides a broader range of symptoms allowing for the possibility of unclear distinction between different DSM mood categories.

Figure 9. Subtypes of the bipolar spectrum suggested by Angst and Gamma [69]



Epidemiology of broadly-defined bipolar disorder

Prevalence rates of bipolar disorders in the population depend to some degree on the choice of diagnostic criteria applied to patients with recurrent depression. Central to this issue is the correct definition of hypomania, which is currently the subject of considerable debate. Three particular areas of controversy are: the minimum duration criterion for hypomanic symptoms (currently 4 days in DSM-IV); the validity of the stem criteria (elevated, expansive or irritable mood); and the correct number of hypomanic signs and symptoms required for a diagnosis of hypomania (currently three or four) (figure 6).

The minimum duration required for a diagnosis of hypomania has changed significantly over the years. In the Research Diagnostic Criteria it was 2 days [70], in DSM-III and DSM-III-R it was not specified, and in DSM-IV it has been set at 4 days. Within the last few years, a group of bipolar experts have recommended reverting back to the threshold of 2 days [71]. The validity of elevated, expansive or irritable mood, the stem criterion A of DSM-IV hypomania, has also recently been questioned. It has been suggested that 'behavioural activation' or periods of overactivity should be given at least the same degree of importance in diagnostic terms as extreme mood symptoms [72]. Finally, at the time of writing, the threshold of three or four out of seven signs and symptoms required for a diagnosis of hypomania has yet to be formally validated.

It is very difficult to assess hypomania in the general population and in depressed patients who tend to be unaware of their elevated mood changes. Unlike most depressives, hypomanic subjects seldom complain of or suffer from their shifts in energy, activity and sleep. It is well known that such changes are more likely first to be picked up and recognised by family and friends. Many of the epidemiological

studies carried out to date have had the disadvantage of assessing symptoms cross-sectionally without corroborative history form patients' families.

Using the Zurich cohort of 4547 young adult subjects, who have now been formally assessed six times between 1978 and 1999, Angst and colleagues recently tested the diagnostic criteria of DSM-IV hypomania and attempted to develop and validate criteria for softer expressions of bipolar II disorder [73]. Clinical validity was assessed by family history, illness course and clinical characteristics, including the association between depression and substance abuse. Three sets of criteria for hypomania were applied to the cohort: DSM-IV hypomania; Zurich 'strict' criteria for hypomania; and Zuirch 'broad' criteria for hypomania. The Zurich 'strict' criteria stipulated that patients suffered from euphoria, irritiability or overactivity, presented with at least 3 of the 7 DSM-IV symptoms of hypomania, had hypomanic symptoms of at least 1 day and experienced negative consequences of hypomania. The 'broad' criteria also stated that patients had euphoria, irritability or overactivity; however, patients had to present with only at least 2 DSM-IV symptoms of hypomania, had no minimum duration of hypomanic symptoms and had no requirement to have experienced negative consequences of hypomania. The prevalence of bipolar II disorder in this cohort was found to be 2% under DSM-IV criteria, 5% under Zurich 'strict' criteria and 11% under Zurich 'broad' criteria. Using the broad criteria suggested that up to 50% of the patients with a major depressive episode may in fact have had bipolar II disorder.

Several additional reports support the finding of a more prevalent and clinically significant spectrum of bipolar disorders. Longitudinal studies of bipolar patients have identified that there are no differences in terms of features such as age at onset, family history of mania or depression and chronicity between patients who

experience hypomanic symptoms for short periods (less than 4 days) compared to patients who have hypomanic symptoms of longer duration [71, 74]. When the duration criterion for hypomania is reduced from 4 to 2 days, the prevalence rate for bipolar disorder rises from 1% to around 5% [75, 76]. Furthermore, when patients with a diagnosis of DSM-IV major depressive disorder (MDD) are systematically assessed for a past history of manic symptoms, 45% satisfy diagnostic criteria for a bipolar disorder [77]. It is also notable that levels of psychosocial impairment and service utilisation are similar between patients with broadly-defined bipolar illness and those diagnosed using DSM-IV criteria [76]. As noted above, this increase in bipolar disorder prevalence occurs at the expense of recurrent depressive disorders, suggesting that between 25% and 50% of all patients with recurrent depression may in fact be part of a bipolar group [69, 78, 79].

Criticisms of the bipolar spectrum concept

Although the concept of a broadened bipolar spectrum has gained some prominence in recent years, it must be noted that this area remains controversial. At the time of writing, a consensus has still to be reached on the correct approach to the assessment and diagnosis of bipolar spectrum conditions. Some authors hold what might be considered to be an extreme view in suggesting that almost all recurrently depressed patients are to some degree bipolar [79-81].

Akiskal and Pinto have suggested that several distinct categories of bipolar disorder exist along a spectrum of severity [82]. These diagnoses have been numbered from bipolar type I to type IV, depending on factors such as previous hospitalisation, a family history of mania, antidepressant-associated hypomania and hyperthymic temperament. In general terms, these categories have not gained

widespread acceptance within research and clinical fields. Many clinicians appear to be uncomfortable with excessive sub-typing of affective disorders.

Baldessarini has argued that classic bipolar disorder is probably as close to a 'disease' as we have in modern psychiatry and that widespread acceptance of broadened definitions of bipolarity run the risk of trivialising the core concept [83]. This view has important implications for biological research into bipolar disorder, including neuropsychological, imaging and genetic studies. It may be the case that research in the genetic field in particular would benefit from the study of more homogeneous and strictly defined sub-types of bipolar disorder (for example, such as puerperal mania [84]. On the other hand, it could be also be argued that most patients with bipolar disorder, as with schizophrenia, are likely to have inherited several different genetic risk factors and that a full understanding of how these factors interact to influence the clinical presentation can only proceed by studying the disorder along a broad clinical spectrum.

Predicting bipolar outcome in apparently unipolar depression

Several factors appear to be associated with conversion to bipolar disorder from unipolar depression. In a three year prospective follow up of 206 consecutive depressed outpatients with no prior history of bipolar disorder, 41 patients (20%) developed an episode of mania [85]. Several variables in this study were associated with bipolar outcome including: depressive episodes of acute onset, frequent recurrence and of brief duration; a positive family history for bipolar disorder; post-partum depression; psychomotor retardation or atypical features; and antidepressant-associated hypomania. The strongest associations with bipolar outcome were for a

positive family history of bipolar disorder and antidepressant-associated hypomania, with positive predictive values of 94% and 100% respectively [85].

Some of these findings have been replicated. In a study of 203 consecutive mood disorder outpatients followed up for between 3 and 6 months, Benazzi reported that bipolar depressives were 3 times more likely to experience antidepressant-associated hypomania than unipolar depressives (17.3% versus 3.8%) [86]. In this study early age at onset of depression and the presence of atypical features were associated with bipolar II disorder and antidepressant-induced switching. In a small study of 27 patients with unipolar depression compared to 27 age and sex-matched patients with bipolar depression, Mitchell and colleagues found that although the two groups did not differ significantly in terms of most of the core symptoms of depression, the bipolar depressed group tended to exhibit less psychomotor slowing, more agitation, more atypical symptoms and had shorter episodes of depression [87].

In the National Institutes of Mental Health (NIMH) collaborative depression study, where patients were followed for 11 years, 48 out of 559 patients converted from unipolar depression to bipolar II bisorder [88]. Early age at onset of depression (defined as onset before age 25), atypical depressive symptoms and recurrent depressive episodes at study entry predicted a switch from unipolar depression to bipolar II disorder. The large French EDIPEP study also showed that early age at onset differentiated bipolar II patients from unipolar patients [78].

A comparison of 39 bipolar I patients with age and sex-matched unipolar patients found that bipolar depressed patients were significantly more likely to have experienced an episode of psychotic depression in the past [59]. Goldberg and colleagues conducted a 15-year follow-up of 74 young adults hospitalised for severe unipolar depression and found that 27% subsequently developed hypomania, with an

additional 19% experiencing at least one episode of full-blown mania [89]. In this study the presence of mood congruent psychotic symptoms, such as auditory hallucinations and delusional beliefs, during the index depressive episode were strongly predictive of bipolar disorder, with eight out of ten patients with psychotic depression eventually becoming bipolar during the 15 year follow-up period [89]. Also of note from this study was that patients with a positive family history of mania were at high risk of a bipolar outcome.

A number of other variables have been associated with bipolar outcome in apparently unipolar patients, although the evidence for these variables is weaker than the factors above. These variables include a premorbid hyperthymic personality, which in some studies [71] but not in others [90] has been associated with a family history of bipolar disorder. Studies of the natural history of mood disorders suggest that bipolar depressive episodes tend to be shorter than unipolar depressive episodes (with mean duration of 3-6 months compared to 6-12 months) [68]. Mostly from clinical observation, it has also been suggested that acute but not prophylactic response to antidepressants (referred to as 'antidepressant wear off') and a history of non-response to multiple courses of antidepressants are additional factors that may be predictive of ultimate bipolar outcome [68].

Ghaemi and colleagues recently suggested that some of the above features could form the basis for a diagnosis of bipolar spectrum disorder (BSD) [91]. BSD would describe a disorder where patients do not meet the strict DSM-IV criteria for bipolar disorder but who nonetheless have clinically significant bipolar features. These criteria are outlined below in figure 10. They emphasise the importance of a first degree family history of bipolar disorder and a personal history of antidepressant-associated hypomania. As noted above, these two factors appear to have the strongest

evidence in terms of being able to predict bipolar outcome. The remaining factors outlined in figure 10 have less evidence in their favour and are therefore given much less weight in terms of the diagnosis of BSD.

These are relatively new criteria and attempts to assess the validity of this diagnosis are currently in progress in a number of centres across the world. In a recent preliminary report, Ghaemi and colleagues applied the BSD criteria to 36 patients with bipolar I or II disorder and 37 unipolar depressives [92]. In a univariate analysis they found that 7 of the 12 features in the BSD criteria were more likely to occur in bipolar than unipolar patients. After adjusting for all predictors in a multivariate regression model, the five most powerful predictors of bipolar disorder were brief major depressive episodes, early age at onset, anti-depressant associated hypomania, postpartum depression and atypical depressive symptoms [92]. In this study the strongest associations were for brief episodes of depression (less than 3 months duration), which had an odds ratio for predicting bipolar disorder of 48.3, and early age at onset (less than age 25) which had an odds ratio of 23.3.

Figure 10. Proposed diagnostic criteria for bipolar spectrum disorder (BSD) [93]

A at least one major depressive episode

B no spontaneous DSM-IV hypomanic or manic episodes

C either of the following plus two from D, or both plus one from D:

- First degree relative with bipolar disorder
- Antidepressant-associated mania or hypomania

D if none from C, at least six of the following:

- Hyperthymic personality
- More than 3 depressive episodes
- Brief major depressive episodes (less than 3 months)
- Atypical depressive symptoms
- Psychotic major depressive episodes
- Early age of onset (less than age 25)
- Postpartum depression
- Antidepressant 'wear-off' (acute but not prophylactic response)
- Lack of response to more than 2 antidepressant trials

Bipolar spectrum disorders in young adults

In most epidemiological studies the age at onset for unipolar major depression is in the late 20s and early 30s, whereas the age at onset for bipolar disorder is consistently identified as occurring between the mid-teens and mid-20s. From the large German Health Interview and Examination Survey (GHS), Jacobi and colleagues have recently demonstrated that 50% of bipolar disorder subjects report an onset before age 18, whereas the median age at onset for major depression is 30 (figure 11) [94].

Figure 11. Age of onset distributions for MDD and BPAD in the GHS [94].

Both early age of onset in depression and severity of depressive episodes are important factors in determining rates of ultimate progression to bipolar disorder. Prepubertal-onset depression may be a strong marker for bipolar disorder, with some studies finding that at least one third of depressed children will develop bipolar disorder in adult life [95]. In a seven-year prospective study of 28 outpatient depressed adolescents Rao and colleagues detected a rate of bipolar outcome of almost 20% [96].

Bipolar disorders tend to present initially in a depressive phase and usually during adolescence or young adulthood [97]. In keeping with the German Health Survey above, the median age of onset of almost 3,000 patients recorded on the Stanley Centre Bipolar Disorder Registry was calculated at 17.5 years [98]. It is also the case that there is often a long delay between the first presentation of a bipolar disorder and diagnosis. In a study of 450 bipolar patients, Baldessarini and colleagues found that mean length of time between first episode and maintenance treatment was 7.8 years [99].

When one considers that rates of progression from adolescent depression to bipolar disorder are in the region of 20% [96, 100], there would appear to be a strong case for consideration of possible bipolar illness in all young adults presenting with recurrent depressive episodes. However, to date this has been an under-studied area. Although the study by Goldberg and colleagues mentioned above prospectively followed young adults hospitalised with depression [89], there are very few studies that have focussed on a cohorts of young adults with recurrent depression in outpatient clinical settings. One of the main aims of this thesis will be to apply the BSD criteria (as defined by Ghaemi and colleagues) to a cohort of young adults with

recurrent depression and to examine the validity of the bipolar spectrum concept in this population both clinically and also in terms of neurocognitive function.

1.3 Neurocognitive function in depression and bipolar disorder

Cognitive dysfunction is a central feature of mood disorders. Both ICD-10 and DSM-IV consider cognitive impairment to be part of the diagnostic criteria for depression and mania. This includes reduced concentration, attention and memory in depression and reduced attention with distractibility in mania. Although it has long been clear that these impairments are present during affective episodes, in recent years it has been recognised that some will also persist upon clinical recovery, often with significant implications for psychosocial functioning [101]. These abnormalities occurring outwith episodes of illness may also provide useful information about the pathophysiology of mood disorders. They can provide information about trait abnormalities (allowing judgements to be made about the neural circuits likely to be underlying mood disorders) as well as permitting assessments of the contribution made by successive episodes of illness to long term psychological functioning.

Many of the studies carried out to date in this area present difficulties for interpretation because they have tended to use populations of patients of differing ages, gender distributions, depressive sub-type (for example, 'mixing in' bipolar and unipolar depressives in the same study), stage of illness (both unwell and recovered) and medication status. Furthermore, although many of the neuropsychological tests used are claimed to represent discrete and anatomically defined functions, the frontal lobes and temporal structures such as the hippocampus and amygdala clearly do not operate in isolation. Strong reciprocal connections between prefrontal and temporo-limbic circuits are well established and abnormalities at one or more points on these circuits could produce many of the findings discussed below.

It is also the case that at the time of writing there were no good quality published studies that directly compare well matched euthymic bipolar patients with euthymic unipolar patients and controls. As a result, most of the conclusions that can be drawn about the differences between cognitive performance in bipolar disorder and unipolar depression have to be extrapolated from case-control studies that compare either bipolar patients or unipolar patients with controls. In reviewing this literature I have organised a critique of the data into two categories: *i)* neurocognitive function in patients with major depressive disorder and *ii)* neurocognitive function in patients with bipolar disorder.

1.3.1 Neurocognitive function in major depressive disorder

Although it had been previously well documented that cognitive impairment was part of the clinical picture of depression [102], it has only been within the last 20 years that studies have assessed the possibility that patterns of neurocognitive impairment in depressed patients might help to identify aspects of the neural circuitry at the core of the disorder.

In an early neuropsychological study, Austin and colleagues compared 40 patients with major depression to 20 age and education-matched controls on a broad neuropsychological battery [103]. They found that depressed patients were more impaired on the auditory verbal learning test. Interestingly, recall and recognition were equally impaired suggesting that effort was not a major determinant of performance. As expected, impairment was positively correlated with depressive symptom scores, even after allowing for the effect of age [103]. This study also found that depressed patients were impaired relative to controls on a test of executive function (the Trail-making test, part B) and that this too was positively correlated with symptom severity [104].

In a similar study of 15 patients with major depression assessed during a depressive episode and compared to 15 age, sex and intelligence-matched controls, Ilsley and colleagues found that the depressed patients were unimpaired relative to controls on measures of short-term memory, recognition, semantic memory and implicit memory. However, depressed patients had deficits in psychomotor speed and in the free recall of material (both immediate and delayed). This selective recall deficit suggests that material had been encoded successfully but that the patients were impaired with regard to search and retrieval processes [105]. A potential limitation of

this study was that 11 of the 14 patients were taking antidepressant medication at the time of testing.

The issue of medication status as a confounding variable in neuropsychological studies of depression was addressed recently by Porter and colleagues [106]. Forty-four patients with major depression, all of whom were carefully assessed as medication free for at least 6 weeks before testing, were compared to 44 demographically matched, healthy comparison subjects. As expected, patients were impaired relative to controls across a broad range of cognitive domains, including attention and executive function and visuospatial learning and memory. Severity of depression correlated with learning and memory performance but not with executive function. This study suggests that appreciable neurocognitive deficits occur during depressive episodes even in medication free patients. Interestingly, in an earlier published report on the same cohort of patients, this research group identified significantly higher cortisol-DHEA ratios in the depressed patients than in the healthy comparison subjects, suggesting that elevated cortisol-DHEA ratios may represent a state marker of depressive illness and contribute to the associated deficits in learning and memory [42].

It should be noted that not all studies of depressed patients have identified neurocognitive impairments. In a large study of 123 depressed patients (who had been medication free for 28 days) and 36 controls, Grant and colleagues failed to detect widespread cognitive impairment apart from executive function deficits on the Wisconsin Card Sort Test [107]. However, this sample of patients, with a mean Hamilton score of 16.7 and mean Beck's score of 17.3 appeared to represent quite a mild clinical sample of depressed outpatients. It is also possible that by comparing

123 patients with only 36 controls the power of this study to detect subtle differences was diminished.

It is well documented that cognitive impairment (and hippocampal volume loss) is more pronounced in older patients with depressive disorder [53, 108-110]. This may be explained by a number of factors, including a greater number of lifetime depressive episodes (and the possibility of a cumulative toxic effect of hypercortisolaemia) [110] or by the influence of microvascular insufficiency or deep white matter hyperintensities in older patients [111, 112]. There remains debate about the mechanism of hippocampal impairment in older depressives. Some studies suggest that acquired biological factors such as microvascular disease may be more important [113] whereas others have suggested that melancholic depressive episodes (which are associated with hypercortisolaemia and which are more common in older adults with depression) is the mechanism of hippocampal volume loss [53, 114].

To date, very few studies have focussed on younger cohorts of depressed patients, although a recent study by MacQueen and colleagues attempted to address this area by examining the function and volume of the hippocampus in a case-control sample of young adults with depression [115]. Twenty never-treated, first-episode depressed subjects were compared to seventeen subjects with a history of multiple episodes of depression and to well matched controls. Hippocampal function was assessed using neuropsychological tests of recollection memory and verbal memory, and hippocampal volume was measured by magnetic resonance imaging. Both first- and multiple-episode depressed groups had impaired hippocampal function as assessed by neuropsychological testing, but only the group with multiple previous episodes had evidence of reduced hippocampal volume. This suggests that reduced

hippocampal volume does not pre-date illness onset but rather may be a consequence of repeated episodes of illness.

Surprisingly, there is a relative paucity of studies examining cognitive function in patients who have recovered from depression. Most of the neuropsychological studies of euthymic or clinically remitted mood disordered patients have been carried out in bipolar subjects (discussed below in the next section). In one study of recovered patients with chronic MDD, Paradiso and colleagues found that patients were more impaired than controls on measures of visual-motor sequencing, executive function, and immediate memory and attention [116]. However, there were important limitations to the design of this study: only 19 patients were compared to 19 controls; only male patients and controls were compared; the threshold for euthymia was set as a Hamilton score of less than 14 (conventionally clinical remission is thought to be consistent with Hamilton scores less than 9); and patients in the study were on relatively high doses of medication (several were on a combination of benzodiazepines, lithium and an antidepressant).

Biringer and colleagues recently re-tested thirty patients who suffered from recurrent major unipolar depression on tests of executive function two years after an initial baseline examination [117]. At baseline patients were depressed (average 17-item HAM-D score 21.8) and at retesting they were partially or totally recovered (average HAM-D score 8.2). There was a significant positive association between improvement on the HAM-D and improvement of executive function. In those patients with complete recovery, executive function was no longer different from the baseline performance of healthy controls. This suggests that recovery from major unipolar depression may be accompanied by a recovery of many aspects of executive function to a normal level.

In summary, the available evidence suggests that currently depressed patients have impairments in the domains of memory, attention and executive function that are to some degree influenced by age, severity of depressive symptoms and previous illness course. These impairments do not appear to be necessarily a function of reduced motivation or effort. Furthermore, they are present to a notable degree in medication-free patients. So far, the evidence suggesting that cognitive impairments persist to any significant degree in unipolar depression beyond clinical recovery is less convincing – this is an area in need of further study.

1.3.2 Neurocognitive function in bipolar disorder

Neurocognitive impairments have been demonstrated across all three phases of bipolar disorder (bipolar depression, euthymia and hypomania/mania) [118]. Perhaps unsurprisingly, the severity of deficits are correlated with earlier age at onset, longer duration of illness, more severe illness episodes and exposure to psychotropics [119]. Although a large number of studies in this area have now been published, many have significant methodological limitations. Neurocognitive findings in each of the three clinical phases of bipolar disorder are reviewed below.

Neurocognitive function in bipolar depression

Bipolar depression and unipolar depression appear to share a similar neuropsychological profile. Although separate studies of unipolar depressives and bipolar depressives compared to controls have identified similar patterns of impairment in attention, memory and executive function [103, 106, 118], very few studies have directly compared bipolar depressed patients with unipolars. Wolfe and colleagues compared four groups on a test of verbal memory and a test of verbal fluency: 20 normal controls, 20 unipolar depressed patients, 12 bipolar depressed patients and 10 patients with Huntington's Disease [120]. They found that both depressed patient groups performed less well than controls on verbal recall and recognition and that bipolar patients were more impaired than unipolar patients on both tasks. Interestingly, the performance of the bipolar patients was similar to that of patients with Huntington's disease, suggesting significant subcortical dysfunction.

The diminished attention seen in bipolar depressed patients (an inattentive response pattern with errors of omission) is similar to that seen in unipolar depressed

patients but is more pronounced [121]. In a relatively large study of consecutively admitted young adult patients, Sweeney and colleagues compared 21 patients with bipolar depression to 58 unipolar depressed patients, 14 manic patients and 51 controls on the computerised Cambridge Neuropsychological Test Automated Battery (CANTAB) [122]. Although manic patients had widespread impairments across verbal memory, attention and executive function domains, bipolar depressed patients and unipolar depressed patients demonstrated only episodic memory impairment relative to controls. As with the study conducted by Wolfe and colleagues [123], the pattern of neuropsychological impairment was similar between bipolar depressives and unipolar depressives.

As with unipolar depression, a number of hypotheses have been suggested to account for the observed cognitive impairment in bipolar depression, including reduced motivation, impaired concentration, slowness of movement and thought, heightened anxiety and hypercortisolaemia. However, whether many these factors are indeed major influences on performance depends to a large extent on whether the observed deficits persist upon clinical recovery. This concept of enduring impairment during phases of recovery in bipolar disorder is considered in detail later in this chapter.

Neurocognitive function in hypomania and mania

Only a small number of studies have assessed the neuropsychological function of hypomanic or manic patients, presumably because of the logistical difficulties in assessing patients during this period of illness. Sax and colleagues used the Continuous Perfomance Test (CPT), a widely used test of sustained attention, to compare 17 manic patients and 13 patients with a mixed affective episode to 13

healthy controls [124]. Both manic groups performed significantly less well than controls, and the mixed mania group performed less well than the pure manic group. In contrast to the pattern of impaired attention seen in bipolar depressed patients (errors of omission) [121], manic patients were characterised by impulsive errors of commission. It is interesting to speculate that this may be reflected clinically in patients with hypomania and mania by a propensity towards impulsivity and poor decision making [125].

In a neuropsychological investigation of prefrontal cortical function in acute mania using selected tests from the CANTAB, Clark and colleagues compared 15 manic patients with 30 normal controls and identified deficits in patients predominantly in verbal memory and sustained attention [126].

The study quoted above by Sweeney and colleagues identified widespread impairments across verbal memory, attention and executive function domains in manic patients compared to controls [122]. Similarly, Martinez-Aran and colleagues compared 30 depressed bipolar patients, 34 manic or hypomanic bipolar patients, 44 euthymic bipolar patients (with euthymia defined as 6 months of remission, a Hamilton depression scale score less than 9, and a Young Mania Rating Scale score less than 7) and 30 healthy controls on a neuropsychological battery assessing executive function, attention, and verbal and visual memory [127]. Unsurprisingly, all three patient groups performed less well than controls across most of the tests. Although both depressed and hypomanic/manic patients performed less well than euthymic patients, there was no clear difference in performance in any of the domains between the depressed bipolars and the hypomanic/manic bipolars.

In summary, the evidence suggests that hypomanic and manic patients have neurocognitive impairments in both verbal memory and attention/executive function.

Furthermore, these deficits appear to be more pronounced in manic patients with mixed affective symptoms or psychotic symptoms [128].

Neurocognitive function in bipolar patients during euthymic intervals

For many years it was believed that euthymic or clinically recovered bipolar patients had an absence of affective symptoms and a normal level of functioning between episodes of illness. However, it has become clear that many bipolar patients will continue to experience sub-syndromal symptoms between episodes of illness that can impact significantly on their social and occupational functioning [129, 130].

A number of studies have now suggested that neurocognitive impairments are present during illness remission. Ferrier and colleagues assessed attention, working memory and executive function in three matched groups of subjects: good-outcome patients with bipolar disorder (n=21); poor-outcome patients with bipolar disorder (n=20); and controls (n=20) [101]. All patients were in clinical remission, although some had low levels of depressive symptoms. Patients performed worse than controls on a number of neuropsychological tests but only the result for executive function (specifically, executive control of working memory) remained significant when age, premorbid IQ and depressive symptoms were controlled for.

In a similar study that used a more rigorous definition of euthymia (clinical remission for at least 4 months), Rubinsztein and colleagues found that compared to controls clinically remitted bipolar patients had a relatively specific impairment in memory (visuospatial recognition) and relatively unimpaired executive function [131]. One interpretation of this finding is that the core deficit in euthymic bipolar disorder lies at the level of temporal structures rather than at the frontal lobe, as suggested by Ferrier and colleagues [101].

In a comparison of 20 euthymic bipolar patients and 20 matched controls, Cavanagh et al found that bipolar patients had impaired verbal memory with relatively intact executive function [132]. However, this study did not control for residual affective symptoms in patients. By contrast, Clark and colleagues found in a similar study that although euthymic bipolar patients were impaired on tasks of attentional set shifting, verbal memory and sustained attention, only the sustained attention deficit remained when mild affective symptoms were controlled for [133]. In a prospectively verified sample of 63 euthymic patients with bipolar disorder and 63 controls, Thompson and colleagues reported a wide range of cognitive deficits, including *both* verbal memory and executive dysfunction [134]. Patients in this study were assessed for over a month as having been euthymic before testing. Salivary cortisol levels were also collected and were found not to be associated with the cognitive deficits.

In a recent functional magnetic resonance imaging study of euthymic bipolar I patients maintained on lithium and compared to controls, Monks and colleagues used two different working memory tasks to explore aspects of working memory function [135]. They found that central executive function, rather than phonological loop function, was the core working memory deficit, suggesting that failure to engage fronto-executive function may be a fundamental neurocognitive deficit in bipolar disorder. It will be interesting to see if this finding can be replicated in medication-free patients.

Although factors such as previous illness severity, number of affective episodes, current levels of mood symptoms and medication status may exert some influence over cognitive performance in bipolar disorder, it may be that the observed deficits in attention/executive function and declarative memory are a function of genetic loading for mood disorder and that they represent trait abnormalities of the

neural circuitry underlying bipolar disorder and depression. This hypothesis can be tested in a number of ways, including twin and family studies, analyses of premorbid functioning in early bipolar illness and assessments of the clinically well first degree relatives of bipolar probands.

Gourovich and colleagues compared neuropsychological performance in seven monozygotic twin pairs who were discordant for bipolar disorder and found that both twins had mnemonic impairments as measured by the Wechsler Memory Scale (WMS) and the California Verbal Learning Test (CVLT), although this study may be confounded by the fact that some of the subjects were tested during an affective episode [136]. In an MRI study of six monozygotic bipolar twins discordant for bipolar disorder and compared to a control group of monozygotic twins with no history of bipolar disorder, Noga and colleagues found that the right hippocampus was smaller in the unwell bipolar twins, but that both ill and well twins had larger caudate nuclei than their control counterparts, suggesting that this structure may be a genetically determined risk factor for the development of bipolar disorder [137]. The role of genetic risk factors is also suggested by a recent finding that patients with bipolar disorder who have a positive family history of psychosis performed worse than patients with no such family history on tests of visual-motor processing and attention [138].

Several retrospective case-control studies suggest that, as appears to be the case in schizophrenia, patients with severe mood disorders have evidence of subtle neurodevelopmental dysfunction in childhood. In a general population birth cohort, Van Os and colleagues found that patients with affective disorders had been delayed in reaching motor milestones and had higher rates of speech abnormalities than normal controls [139]. Similarly, higher rates of developmental impairments in

language, motor and social functioning have been found in adolescents with bipolar disorder or depressive psychosis relative to unaffected controls [140]. In a prospective study that followed 56 children with deficits in attention, motor control and perception ('DAMP') and controls between the ages of 6 and 16, Hellgren and colleagues found that the DAMP group had higher rates of psychiatric disorder, especially major depression, at follow up [141].

Several studies have now identified neurocognitive abnormalities in the unaffected family members of bipolar patients. In an examination of neuropsychological performance in the family members of patients with schizophrenia and bipolar disorder, Keri and colleagues found that the unaffected relatives of the bipolar group had more verbal recall difficulties than a group of unrelated controls [142]. Zalla and colleagues have reported that both bipolar patients and their unaffected relatives are impaired on the Stroop test, suggesting a trait deficit in prefrontal attention and executive function [143]. More recently, a study of 17 euthymic bipolar patients and 17 unaffected first degree relatives identified selective deficits in declarative memory and executive control in relatives [144].

Taken together, the studies reviewed above suggest that the cognitive profile of bipolar disorder may be characterised by persistent deficits in either declarative memory abilities, executive function or both. Although previous illness course, current affective symptoms and medication may play a role in these deficits, they may also represent trait abnormalities that are closely related to genetic risk. In other words, these neurocognitive impairments may reflect underlying endophenotypic abnormalities that are central to the pathophysiology of bipolar disorder [145].

1.3.3 Methodological considerations

It can be seen from the above that the literature of neuropsychological testing in mood disorders as it currently stands has a number of limitations that will need to be addressed in future studies. These limitations are now considered in more detail.

Medication effects

Neuropsychological studies on drug naïve patients with mood disorder are relatively rare because of the difficulties in recruiting patients who are medication-free. It may also be unethical to conduct studies that require patients to be drug-free for long periods. It is well documented that psychotropic medications may influence performance on cognitive tests [146]. Neuroleptics (particularly traditional antipsychotics such a chlorpromazine) and benzodiazepines have been shown to have a detrimental effect on cognitive function [147]. Antidepressants, especially those with anticholinergic properties, have been associated with subtle deficits in psychomotor speed and verbal memory [129, 148]. In some studies lithium has been reported to have adverse effects on memory and psychomotor functioning [149] whereas in others it has been shown to be relatively benign [150, 151]. During a 6 year follow-up period of lithium-treated bipolar patients, Engelsmann and colleagues found no evidence of cognitive decline [151]. More recently, the possibility has emerged that mood stabilisers such as lithium and valproate may actually enhance cognitive function through a neuroprotective action on neuronal tissue [152].

Even though several authors have suggested that the effects of psychotropic medications are relatively minor, it must be acknowledged that even small effects could substantially detract from the conclusions of many studies because the

differences detected between patients and controls are often of quite a small magnitude. It also the case that many patients will have been taking combinations of psychotropic medications at varying doses over long time periods. The true effect of combined medication (for example, antidepressants plus mood stabilisers) is currently unknown.

Sample size and heterogeneity

Many studies in this field are underpowered because of small sample sizes. It is also clear that when there are adequate numbers of patients and controls, it is often the case that the patient group were heterogeneous in terms of age, clinical subtype and previous course of illness. This is particularly important in those studies that include patients with psychotic symptoms and non-psychotic patients in the same group. Even though alcohol abuse occurs in up to 50% of patients with bipolar disorder [68] (and is well recognised as a cause of cognitive impairment), too few studies stipulate a history of significant alcohol misuse as an exclusion criterion.

Effect sizes and degree of functional impairment

Although neuropsychological studies often detect statistically significant differences between patients and controls, many of these differences are relatively small and may not necessarily be related to significant functional deficits. Over the last few years it has increasingly been the case that measures of effect sizes are reported so that a more meaningful estimation of the degree of cognitive deficit can be appreciated [134].

The correct definition of euthymia

Unfortunately, until relatively recently, many studies have used definitions of euthymia that may be inadequate. The true definition of sustained clinical recovery in bipolar disorder remains extremely difficult, especially in light of recent evidence suggesting that residual affective symptoms (and functional impairment) is common throughout the natural history of bipolar disorder [74]. Until an accepted definition of euthymia is agreed, it seems that current best practice would be to use samples of patients who have been prospectively assessed (both subjectively and objectively) as being in full clinical remission for at least a period of 3 months.

Diagnostic considerations

As discussed in the first half of this chapter, there is debate about the boundaries between recurrent major depression, bipolar spectrum disorder, bipolar II disorder and bipolar I disorder. Many neuropsychological studies of depression and bipolar disorder have 'mixed in' unipolar depressives with bipolar I depressives and bipolar II depressives. Future studies may benefit from the use of more diagnostically homogeneous patient groups.

Do neuropsychological impairments reflect disease process or trait deficits?

Some of the studies noted above have identified correlations between illness variables such as number of previous affective episodes or more severe affective episodes (eg, psychotic episodes) and degree of neurocognitive impairment [119, 132]. This has been hypothesised as being due to an ongoing disease process, for example, the toxic effects of hypercortisolaemia during acute exacerbations having a 'scarring' effect on vulnerable brain regions such as the hippocampus [132]. However, as also discussed

above, there is also converging evidence from a number of studies that these abnormalities may represent trait, or endophenotypic, deficits. Future 'high risk' paradigms (for example, assessing clinically well first degree relatives or prodromal patients), as well as prospective neuropsychological assessments on patients, will be required to separate out the effects of 'state' and 'scar' from trait or genetic vulnerabilities.

1.3.4 Implications of neurocognitive impairment for the aetiology and pathophysiology of depression and bipolar disorder

Despite limitations within many of the neuropsychological studies of mood disorder, some of the more robust findings (that is, attention/working memory, executive function and declarative memory deficits) are supported by neuroimaging studies.

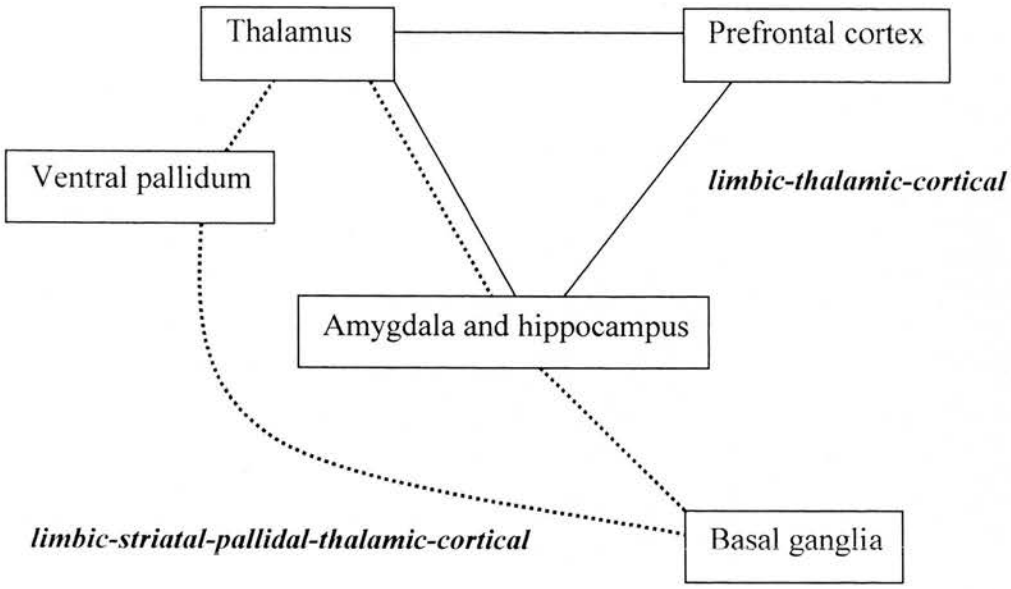
One of the most consistent imaging findings in mood disorders has been a reduction in brain volume and blood flow within the dorsolateral prefrontal cortex in both unipolar and bipolar disorder [153-156]. The anterior cingulate cortex has been consistently implicated in functional imaging studies of depression [157, 158] and reduced size of the hippocampus has been identified for both depression and bipolar disorder [159-161]. Although subcortical and medial temporal structures such as the basal ganglia and amygdala are reduced in size in unipolar depressive disorder [154, 162], several studies have demonstrated an enlargement of these structures in bipolar disorder [161, 163]. This difference raises the possibility that subcortical abnormalities in mood disorders may be responsible for the phenotypic distinction between bipolar disorder and unipolar disorder. It has been suggested that unipolar depression and bipolar disorder may share a common 'underdevelopment' of the prefrontal region, leading to a loss of inhibitory cortical control over limbic emotional networks [56]. The expression of a mood disorder as either unipolar or bipolar may then be dependant upon whether these limbic structures (basal ganglia or amygdala) are smaller or larger than normal [164].

The principal goal of neuropsychological and neuroimaging research in mood disorders is to understand the fundamental abnormalities of neural circuitry that are dysfunctional in individuals who suffer from depressive disorders. From the studies

reviewed above, it is possible to speculate on the neurocircuitry involved in depressive disorders. Soares and Mann [165] have suggested that the brain regions outlined in figure 12 are involved in the modulation of mood and that two interconnecting circuits are central to the pathophysiology of mood disorders. These are a *'limbic-thalamic-cortical'* circuit (connecting the amygdala, the mediodorsal thalamic nucleus, and the medial and ventrolateral prefrontal cortex) and a *'limbic-striatal-pallidal-thalamic-cortical'* circuit (connecting the limbic system with the basal ganglia and thalamus). Affective disturbance is thought to result from dysfunction at one or points on these circuits.

Neuropsychological research in mood disorders also has the potential to contribute to aetiological investigations, for example, by correlating endophenotypic cognitive deficits with putative genetic risk factors. Of particular relevance for this thesis is the question of whether neurocognitive performance in mood-disordered patients can be used to assess the validity of both established and novel diagnostic criteria for depression and bipolar spectrum disorder.

Figure 12. Brain regions implicated in the regulation of mood



1.4 Objectives

In the introduction above I have reviewed the aetiology, pathophysiology, classification and neuropsychology of mood disorders. In terms of classification, I have highlighted the concept of a broadened bipolar spectrum, including a discussion of the background to the recent proposal of novel diagnostic criteria for bipolar spectrum disorder (BSD) (figure 10) [93]. Factors such as early onset of depression (that is, in adolescence or young adulthood) and severe depressive episodes are strongly associated with both high genetic loading for mood disorder and a high risk for lifetime progression to bipolar disorder. It follows that a useful sub-group of depressives to study with regards to the validity of a broadened bipolar spectrum is a cohort of young adults with early-onset recurrent depression.

1.4.1 Prevalence and validity of BSD criteria in young adults with early-onset recurrent depression

The first aim of this thesis is to assess the clinical presentation of recurrent depression in young adults with particular reference to the prevalence of bipolar spectrum disorders within this group. An attempt will then be made to assess the validity of the BSD criteria according to clinical parameters. The classic guidelines for establishing the validity of psychiatric diagnoses proposed by Robins and Guze will be used [166]. These include: clinical phenomenology; clinical course; family history; and treatment response. Patients with DSM-IV defined BPAD will be compared to BSD patients (defined according to figure 10) and DSM-IV MDD patients on each of these validity criteria.

1.4.2 Neurocognitive function in young adults with MDD and BSD

In reviewing the neurocognitive literature on mood disorders, there appears to be good evidence that trait deficits in attention, executive function and declarative memory are present in both unipolar depression and bipolar disorder. Furthermore, these traits are more prominent in bipolar disorders than unipolar disorders, perhaps as a consequence of higher genetic loading for mood disorder in the bipolar group (although, as discussed above, there is debate about the degree to which these deficits are truly endophenotypic because of factors such as previous illness course and residual mood symptoms). A current deficiency in the neuropsychological literature of mood disorders is the paucity of studies that directly compare well-matched groups of young unipolar and bipolar patients, especially during periods of euthymia.

The second aim of this thesis is therefore to provide a comparison of neurocognitive performance between euthymic young adults with DSM-IV recurrent MDD, euthymic young adults with bipolar spectrum disorder (BSD) and well-matched young adult controls. If one accepts that young adults with recurrent depression who appear to have an early bipolar illness are likely to have a strong genetic predisposition to mood disorder, this study can add to the debate about the relative contributions made to cognitive impairment in mood disorders by genetic risk factors and/or clinical factors such as illness severity or repeated episodes of illness.

Also as part of this neuropsychological study, I will consider the implications for the concept of a broadened bipolar spectrum of the similarities and differences in neurocognitive performance between young patients with DSM-IV major depression and young adults with BSD. This will permit a consideration of whether cognitive

function in the euthymic state can be used indirectly to assess the validity of the BSD diagnostic criteria.

Chapter 2 Methods

2.1 Outline of study

2.2 Recruitment of patients and controls

2.3 Data collection

2.3.1 Diagnostic assessments

2.3.2 Neurocognitive testing

2.4 Statistical analyses

2.4.1 Analyses of descriptive clinical and diagnostic data

2.4.2 Analyses of neuropsychological test data

2.1 Outline of study

The primary aims of this study were two-fold: firstly, to provide a detailed clinical description of recurrent depression in young adults with particular reference to bipolar spectrum disorders; and secondly, to perform a neurocognitive study comparing euthymic young adults with major depressive disorder (MDD), bipolar spectrum disorder (BSD) and controls. This work was carried out in the Division of Psychiatry at the University of Edinburgh between 2002 and 2004.

2.2 Recruitment of patients and controls

Figure 13 outlines how different stages of this study were conducted. Recruitment of patients and controls was carried out during a 12 month period. All patients were recruited from a psychiatric clinic at the University of Edinburgh Student Health Service (SHS). Over 90% of students at Edinburgh University are registered at this practice.

Ethics approval

All of the work carried out in this project was approved by the Lothian Research Ethics Committee and all participants provided full informed written consent from the beginning.

Screening assessment

Between July 2002 and July 2003 a total of 234 referrals were made by General Practitioners (GPs) at the SHS to the psychiatric clinic. These referrals were screened

by Professor Douglas Blackwood (D.B.) and myself (D.S.) during a standard clinical assessment interview. At this point the inclusion and exclusion criteria were applied.

Inclusion and exclusion criteria

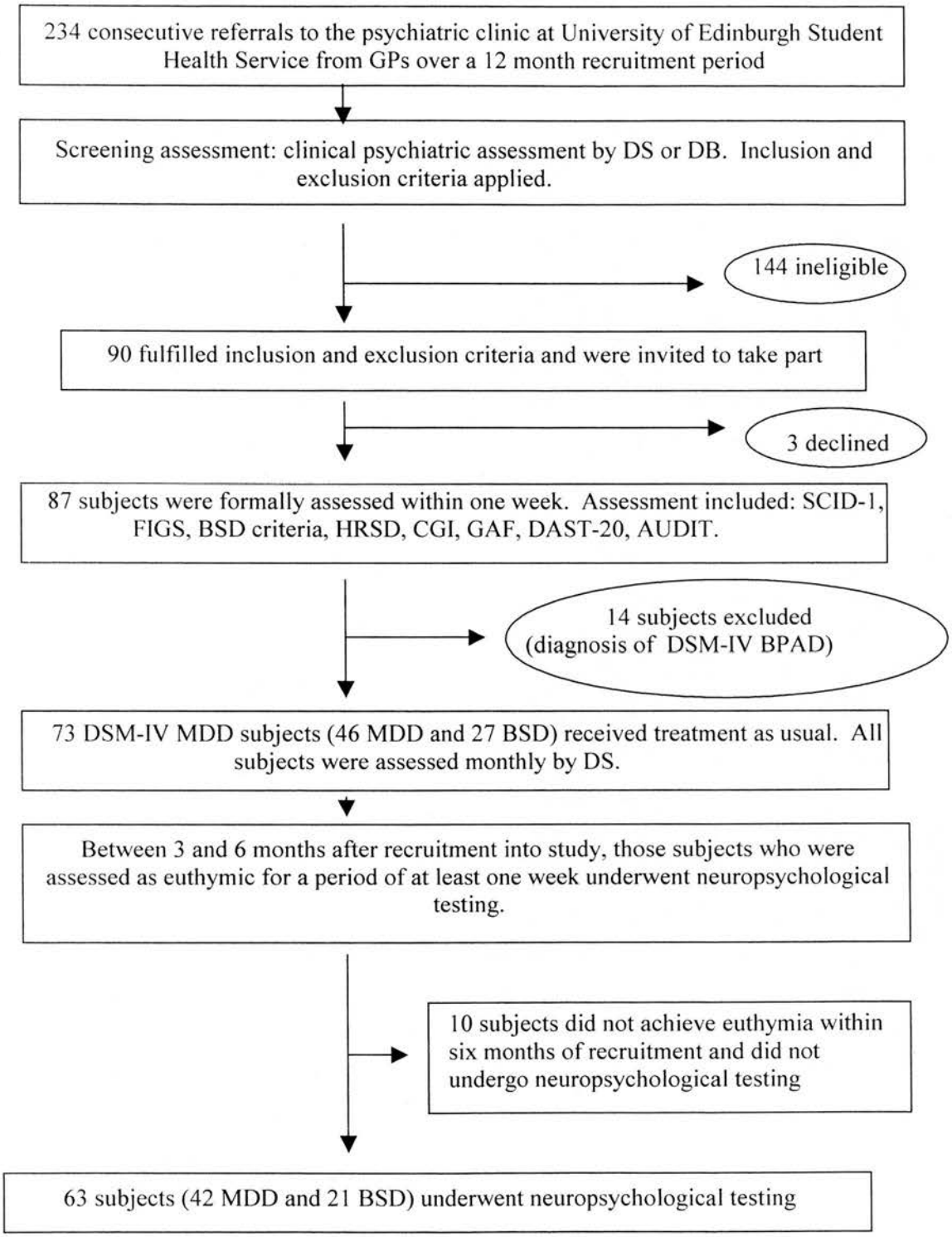
The main inclusion criterion was a current episode of DSM-IV major depressive disorder (MDD) and at least one previous DSM-IV major depressive episode (MDE), with onset of illness before age 22. This age limit was set for two reasons. Firstly, previous work suggests that this age threshold defines a strongly genetic sub-type of depressive disorder. Secondly, this study chose to assess bipolar spectrum disorders in young patients with an early-onset of depression and a history of recurrent depression because these factors have been linked to the ultimate development of bipolar disorder.

Patients were excluded if they had a history of previous head injury, epilepsy or another medical disorder. From the original 234 referrals to the clinic, 144 were assessed as ineligible to participate (figure 13). Ninety patients satisfied the inclusion and exclusion criteria and were asked to take part in the study. Eighty seven agreed and provided written consent.

Controls

Patients participating in the study were asked to volunteer friends of a similar age, gender, socioeconomic background and who had no personal history of depression to act as controls. A total of 33 controls were recruited in this way.

Figure 13. Outline of study



2.3 Data collection

All subsequent descriptive, diagnostic and experimental data was collected by D.S.

2.3.1 Diagnostic assessments

All patients who agreed to take part underwent formal assessment within one week. Illness characteristics (including age-at-onset, number of affective episodes, history of deliberate self-harm, and past suicidal behaviour) were derived from retrospective life charts constructed from the assessment interview and medical records [167]. Social class was defined according to father's occupation [168]. In addition to the assessment interview, formal DSM-IV diagnoses were obtained on patients and controls using the Structured Clinical Interview for DSM-IV (SCID-1) [169]. This is a widely used and validated diagnostic instrument that generates diagnoses according to DSM-IV. It is a standardised interviewer-led assessment tool and D.S. has been trained in its use. In addition to the DSM-IV diagnosis, the novel structured diagnostic criteria for BSD (figure 10) [93] were also applied to all patients. The definition of 'hyperthymia' was based on the criteria outlined in figure 14 and the definition of 'antidepressant-associated hypomania' was hypomania or mania diagnosed according to DSM-IV criteria (as outlined in figure 6).

According to the Structured Diagnostic Interview for DSM-IV (SCID-1) [169], 14 patients had bipolar affective disorder (4 had bipolar I disorder and 10 had bipolar II disorder). Seventy three patients had recurrent MDD. Twenty four of the 73 MDD patients also satisfied the diagnostic criteria for BSD. Only these 73 patients (46 MDD and 27 BSD) were assessed further, as below.

Figure 14. Hyperthymic temperament

At least 4 out of the following 6 habitual traits:

1 cheerful, over-optimistic or exuberant
2 extroverted and people-seeking
3 over-talkative, eloquent and jocular
4 uninhibited, stimulus-seeking and sexually-driven
5 vigorous, full of plans, improvident
6 overconfident, self-assured and boastful

Family history data were obtained using the Family Interview for Genetic Studies (FIGS) [170]. The FIGS is a structured diagnostic instrument that has been developed by the National Institutes for Mental Health in the United States. It is a validated instrument that is widely used in psychiatric genetics research [170]. Again, D.S. has been trained in its use.

Drug and alcohol use during the preceding 12 months were assessed by the 20-item Drug Abuse Screening Test (DAST-20; [171]) and the Alcohol Use Disorders Identification Test (AUDIT; [172]). The DAST-20 is a well validated [173] questionnaire where subjects are asked questions about their drug use during the preceding 12 months. Overall scores (from 0 to 20) are generated allocating the patient to one of five categories, from 'no drug use' to 'severe level of drug use'.

The AUDIT is a brief structured interview developed by the World Health Organisation (WHO) that can be incorporated into a psychiatric assessment. It contains questions about recent alcohol consumption, dependence symptoms, and alcohol-related symptoms. There are ten stems with each scored between 0-4. An overall score of 8 or more is considered positive for screening and the maximum possible score is 40. The AUDIT was recently demonstrated to be a valid tool for the detection of alcohol use disorders in a student population [174].

Symptom severity was assessed by the 21-item Hamilton Rating Scale for Depression, (HRSD) [175] and the Clinical Global Impression of Illness scale (CGI) [176]. Psychosocial impairment during the preceding 12 months was rated using the Global Assessment of Functioning scale [177]. Further details of all assessment instruments are included within the Appendix.

All 73 patients in the study received treatment as usual in the psychiatric clinic and from their GPs. This included both medication and, for a small number of patients, cognitive and behavioural therapy. All were seen on at least a monthly basis by D.S. for clinical review.

Between 3 and 6 months after recruitment into the study, those patients who were assessed as being in clinical remission for at least one month went forward to the next stage of the study (neuropsychological assessment). Euthymia was defined as a HRSD score of less than or equal to 8. This threshold is recognised as a measure of clinical remission in depression [175] and has been widely used as a definition of euthymia in several neuropsychological studies of this kind [115, 127, 132, 133]. Ten patients did not achieve clinical remission within six months of recruitment and therefore did not undergo neuropsychological testing. In total, 63 patients (42 MDD and 21 BSD) and 33 controls underwent neuropsychological testing.

2.3.2 Neurocognitive testing

All patients and controls were assessed by D.S. using a comprehensive fixed-order test battery spanning two principal cognitive domains (verbal memory and attention/executive function). All subjects were assessed at 2pm to control for the effects of diurnal variation on performance. Tests were administered according to standard instructions and took approximately 60 minutes to complete. All tests were

completed using pencil and paper methods. Full details of the neuropsychological tests are included within the Appendix.

An estimate of premorbid levels of intellectual functioning was obtained by using a combination of three factors: number of years in education; the National Adult Reading Test (NART) score [178]; and the block-design sub-test of the Wechsler Adult Intelligence Scale, revised (WAIS-R) [179]. Although the NART and the block design sub-test of the WAIS are not formal IQ tests, this combination of factors has been widely used in neuropsychological studies to compare patient and control groups. An assessment of handedness was also obtained for subjects and controls using the Annett Handedness Inventory [180]. The instruments used to assess each neurocognitive domain were as follows:

a) **Verbal learning and memory:**

California Verbal Learning Test (CVLT)

The California Verbal Learning Test (CVLT) [181] is an auditory verbal memory test using a 16-item shopping list ('list A') that is read to the subject five times. After each trial of the list read by the investigator, subjects must repeat back as many items as they can remember. This produces a score for each of the 5 learning trials (trials 1 to 5) as well as a list A total score (trials 1-5 summed). A second shopping list ('list B') is then read to the subjects and they are asked to recall these items. Immediately after this, subjects are asked to recall the items from list A again (free short delay recall). Subjects are then prompted to try to recall the items on list A by being prompted with cues, including 'spices and herbs', 'tools', 'clothing' and 'friut' (cued short recall 1-4). A non-verbal test then follows lasting 20 minutes (in this battery,

the WAIS-R, Brixton Spatial Anticipation Test and the Trail-making Test parts A and B) and free (non-cued) long-delay recall of list A is then re-assessed. This is followed by a repeat of the 4 cued categories and a test of recognition of list A items (recogniton hits).

b) Attention and executive function:

Trail-making Test

The Trail-making Test, TMT, consists of two parts, A and B [104]. The TMT-A requires an individual to draw lines sequentially connecting 25 encircled numbers distributed on a sheet of paper. As such, TMT-A can be considered a test of attention. The task requirements are similar in TMT-B except the person must now connect between numbers and letters alternately and in ascending order (i.e., 1, A, 2, B, 3, C, etc.). The TMT-B is considered a test of set-shifting ability.

Brixton Spatial Anticipation Test

The Brixton Spatial Anticipation Test (BSAT) [182] is a test of executive function consisting of a 56 page stimulus book. Each page shows the same basic array of ten circles set in two rows of five, with each circle numbered from one to ten. On each page one of the circles is filled in with the colour blue. The position of this filled circle changes on most presentations from page to page. The subject is shown one page at a time and asked to predict where the next filled position will be, based on what they have seen on previous pages. The Brixton test is a concept or 'rule attainment' test and is very similar to (but shorter than) the more widely known Wisconsin Card Sorting Test.

Stroop Colour Word Test

The Stroop Colour Word Test [183] is a test of executive function that involves an initial 'priming' trial of reading aloud a list of colours written in incongruously coloured ink (Stroop Colour). This is followed by a second 'colour-word' trial reading aloud a second list of colour names in incongruous coloured ink but this time naming the colour of the ink rather than the word (Stroop Colour-Word). The number of correct responses is calculated as the number of colours correctly identified minus the number of incorrect responses.

2.4 Statistical Analyses

All statistical analyses were performed by D.S. using the Statistical Package for the Social Sciences, version 12 [184].

2.4.1 Analyses of descriptive clinical and diagnostic data

Given that most of these data were descriptive and exploratory, only limited statistical testing was carried out. Where formal analyses were conducted, patient groups (MDD versus BSD) were compared on baseline demographic and clinical characteristics using independent *t*-tests for continuously distributed variables and with chi-squared tests for categorical data. Two-tailed significance for these analyses was set at $p<0.05$. This was considered appropriate given the relatively small number of comparisons carried out in this section. When a statistically significant finding emerged on the chi-squared tests, odds ratios were also calculated in order to quantify the magnitude of difference between groups.

An additional analysis was conducted on four subject groups (MDD, BSD, BPAD and controls) for selected clinical variables by using ANOVA with the post hoc Tukey honestly significant different (HSD) test for continuous data and chi-squared tests for categorical data.

2.4.2 Analyses of neuropsychological test data

Baseline demographic and clinical characteristics

For continuous variables groups were compared on clinical and demographic characteristics by using analysis of variance (ANOVA) for comparisons between 3 groups (MDD, BSD and controls) and independent *t*-tests for comparisons between 2 groups (MDD versus BSD). The chi-squared test was used to compare categorical variables.

Neuropsychological tests

Performance on neuropsychological tests was compared across the three groups (MDD, BSD and controls) by means of multivariate analysis of variance (MANOVA). As many of the neuropsychological tests used in this study are naturally correlated, this procedure was considered superior to a Bonferroni inequality correction because the latter would tend to increase type II error. A further MANOVA analysis was performed with gender as a 'between subjects' factor, and with estimated premorbid intelligence (NART score), age and HRSD scores as covariates. Diagnostic group (MDD, BSD or controls) was the main factor. These covariates and the 'between subjects' factor were included in the analysis because of the possibility that even

small differences on these variables between groups could contribute to differences observed on neuropsychological testing.

Where significant main effects were detected on MANOVA, group differences between MDD patients, BSD patients, and controls were then tested in a one-way ANOVA, followed by a Tukey honestly significant difference (HSD) post hoc comparison. A two-tailed significance level was set at $p<0.05$.

In order to place the observed differences between groups into a more meaningful context, three further analyses were performed: calculation of effect sizes; estimation of the proportion of MDD and BSD patients scoring on or below the fifth percentile of controls; and correlations between test scores that showed statistically significant group differences and the clinical variables of age at onset and number of previous depressive episodes.

After Howell [185], estimates of effect size were calculated using the formula:

$$(\mu_{patients}-\mu_{controls})/\sigma_{pooled}$$

The first part of this equation was reversed for tasks where a high score indicates poorer performance (i.e. $\mu_{controls}-\mu_{patients}$) to standardise the scoring schemes across tasks. The Cohen convention for small and large effect sizes was used: small effect size as less than or equal to 0.5; medium effect size as greater than 0.5 and less than 0.8; and large effect size as equal to or greater than 0.8 [186].

The proportion of MDD and BSD patients scoring on or below the fifth percentile was determined by calculating the percentage of patients scoring –1.64 standard deviations from the mean of the control sample.

Correlations between those neuropsychological test scores that showed statistically significant group differences and clinical variables (that is, age at onset

and number of previous depressive episodes) were tested for the MDD and BSD groups separately with Pearson correlations. A two-tailed significance level of $p<0.05$ was also set for these analyses.

Chapter 3 Results

3.1 Prevalence and validity of BSD criteria in young adults with early-onset recurrent depression

3.1.1 Diagnostic composition of patient sample

3.1.2 Demographic and clinical characteristics of the sample

3.2 Neurocognitive function in young adults with MDD and BSD

3.2.1 Baseline demographic and clinical characteristics compared

3.2.2 Neurocognitive function results

3.2.3 Correlations between illness characteristics and neurocognitive performance

3.1 Prevalence and validity of BSD criteria in young adults with early-onset recurrent depression.

3.1.1 Diagnostic composition of patient sample

From the 87 patients who were included in the study, 14 (16.1%) fulfilled DSM-IV criteria for bipolar affective disorder (4 had bipolar I disorder and 10 had bipolar II disorder). The remaining 73 patients (83.9%) had DSM-IV recurrent MDD. Twenty seven of these satisfied the diagnostic criteria for BSD, leaving a group of 46 patients with recurrent MDD. Figure 15 illustrates the diagnostic composition of this patient sample (46 MDD, 27 BSD and 14 BPAD). If we accept that a BSD diagnosis in this relatively young patient group may represent a developing bipolar illness, then 41 (47.1%) of the patients in this consecutively recruited sample might be considered to have a broadly-defined bipolar disorder.

Figure 15. Diagnostic composition of cohort

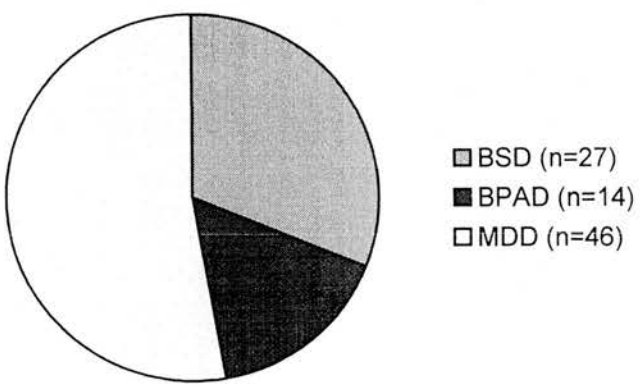


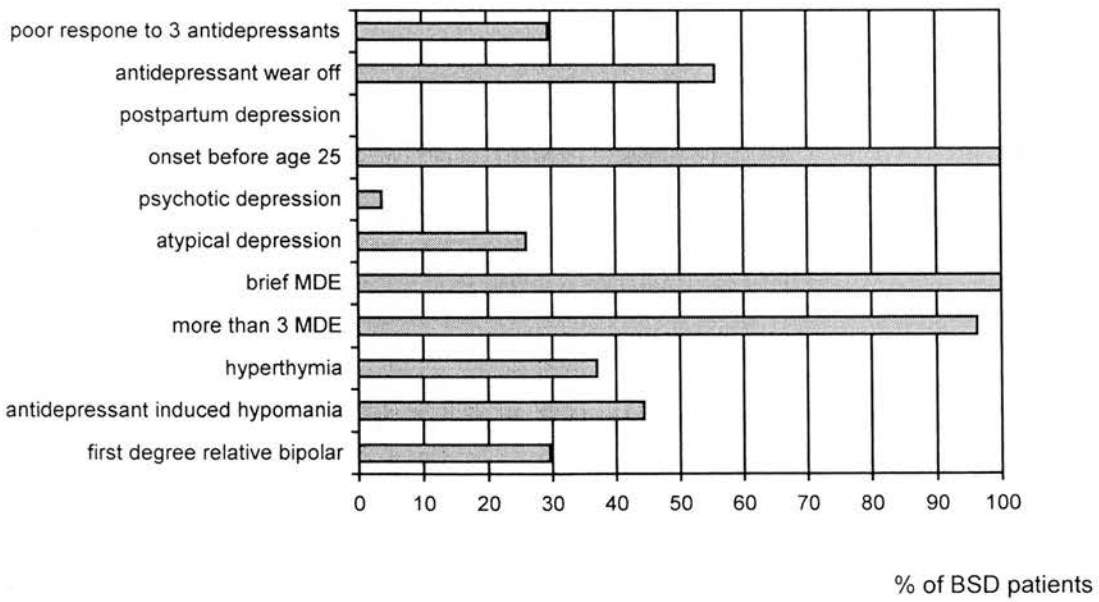
Figure 16. Frequency of 'core' BSD criteria in BSD patients (n=27)

BSD criterion	Number	(%)
A First degree relative with bipolar disorder	8	29.6
B Antidepressant-associated hypomania	12	44.4
Either A or B present	19	70.4
Both A and B present	1	3.7
Neither A nor B present	8	29.6

Figures 16 and 17 show the relative frequencies of the BSD criteria in the 27 patients who satisfied this diagnosis. In figure 16, it can be seen that 19 of these patients (70%) had at least one of the core criteria (that is, either a first degree relative with bipolar disorder or a past history of antidepressant-associated hypomania). This leaves the remaining 8 patients (30%) fulfilling the BSD criteria by virtue of having none of these two core criteria but at least 6 of the 9 secondary criteria outlined in figure 10. As noted above in the introduction chapter, the two core criteria are given much greater weight diagnostically because of the strength of the evidence that suggests these features are more strongly associated with bipolar outcome in recurrent depression.

Figure 17 provides a more detailed view of the relative frequencies of each of the criteria in the BSD patients. Of particular note is the fact that 12 patients (44%) had a history of antidepressant-associated hypomania and 8 (30%) had at least one first degree relative with bipolar disorder. Only one patient (3.7%) had psychotic depression and 7 patients (26%) had atypical depression. All of the patients satisfied the criteria of age of onset before age 25 because of the inclusion criteria for this study. Similarly, none of the patients had a history of postpartum depression, again because this sample were relatively young and were recruited from a student population. All of the BSD patients reported brief episodes of depression (lasting less than 3 months) and almost all (96%) had experienced more than 3 episodes.

Figure 17. Frequencies of BSD criteria (n=27)



3.1.2 Demographic and clinical characteristics of the sample

Demographic characteristics of the sample

Table 1 outlines the demographic characteristics of the patient and control samples. Of particular note is the young age of this cohort (mean age 22 years), the relatively homogeneous ethnic composition and the relatively high social class. Although these characteristics are related to the setting of this study and the inclusion and exclusion criteria that were used, they may represent study strengths in terms of interpreting the neurocognitive analyses that follow. It can be seen that all three patient groups and the control group were closely matched on all of the demographic variables.

Table 1. Demographic characteristics

Characteristic	MDD n=46	BSD n=27	BPAD n=14	Controls n=33
Gender, N (%): Females	32 (70)	16 (59)	11 (79)	19 (58)
Ethnicity, N (%): Caucasian Other	45 (98) 1 (2)	25 (93) 2 (7)	13 (93) 1 (7)	31 (94) 2 (6)
Age: mean (SD)	21.6 (2.20)	22.8 (3.01)	21.7 (2.97)	22.2 (2.29)
Marital Status, N (%): Single Married/living with partner	41 (89) 5 (11)	26 (96) 1 (4)	14 (100) 0 (0)	31 (94) 2 (6)
Social class I II III	42 (91) 3 (7) 1 (2)	19 (70) 7 (26) 1 (4)	13 (93) 1 (7) 0 (0)	30 (91) 3 (9) 0 (0)
Years of full-time education: Mean (SD)	16.7 (1.56)	17.0 (1.73)	16.7 (1.67)	17.3 (1.40)

Clinical characteristics of the sample

Table 2 contains the information that was gathered on the clinical characteristics of patients and controls.

Table 2. Clinical characteristics

Characteristic		MDD n=46	BSD n=27	BPAD n=14	Controls n=33
Family history: first degree relative with: depression	*N (%)*	33 (71.7)	22 (81.5)	11 (78.6)	12 (36.4)
bipolar disorder	*N (%)*	0 (0)	8 (29.6)	3 (21.4)	0 (0)
Antidepressant -associated hypomania	*mean (SD)*	0 (0)	12 (44.4)	6 (42.9)	---
Age-at-onset	*mean (SD)*	15.7 (2.61)	15.0 (2.77)	14.7 (1.44)	---
Number of depressive episodes	*mean (SD)*	4.0 (1.46)	4.7 (1.42)	3.8 (1.40)	---
Index episode atypical depression	*N (%)*	4 (8.7)	7 (26.0)	1 (7.1)	---
HRSD	*mean (SD)*	26.5 (4.60)	27.3 (4.81)	29.7 (4.58)	---
CGI score	*mean (SD)*	4.1 (0.28)	4.3 (0.53)	4.3 (0.47)	---
GAF score	*mean (SD)*	52.9 (5.89)	53.7 (5.56)	51.4 (5.65)	---
History of deliberate self-harm	*N (%)*	20 (43.5)	16 (59.3)	10 (71.4)	0 (0)
Previous suicide attempt	*N (%)*	6 (19.6)	7 (26.0)	4 (28.6)	0 (0)
DAST-20 score	*mean (SD)*	0.9 (1.09)	1.3 (1.32)	3.1 (3.39)	1.8 (1.02)
AUDIT score	*mean (SD)*	9.2 (5.65)	12.4 (8.26)	10.9 (8.00)	8.5 (6.56)

Table 2 permits a preliminary analysis of the clinical validity of the BSD criteria according to the categories suggested by Robins and Guze [166]. A key issue is whether the BSD group appears to be similar to the BPAD group (and sufficiently different from the MDD group) on measures of clinical phenomenology, clinical course, family history and treatment response. The principal findings in this regard are presented below and are considered in more detail within the discussion chapter.

a) Clinical phenomenology

Across all three patient groups (MDD, BSD and BPAD) there were no significant differences in terms of severity of the index depressive episode (HRSD and CGI scores) or levels of psychosocial functioning as measured by GAF scores (table 2). However, significantly more of the BSD patients reported atypical depression as the index depressive episode (26.0% in BSD patients compared to 8.7% in MDD patients; $X^2=3.95$, df=1, $p<0.05$). This is an interesting finding in the light of work suggesting that atypical depression (which includes symptoms such as extreme fatigue, hypersomnia, hyperphagia and sensitivity to rejection) may be more common in bipolar depression than unipolar depression [59, 187]. It must be acknowledged, however, that only 1 of the 14 BPAD patients (7%) had an atypical index depressive episode.

There was a non-significant trend towards higher rates of deliberate self-harm and suicidal behaviour in both bipolar groups compared to the MDD group (table 2). 71% of the BPAD patients had harmed themselves in some way in the past compared to 59% in the BSD group and 44% in the MDD group. Similarly, rates of at least one previous suicide attempt were 29% in the BPAD group, 26% in the BSD group and 20% in the MDD group.

Levels of reported drug use in this study were lower than anticipated, probably as a result of under-reporting. Other reasons for this are considered more fully within the discussion chapter. Although the maximum possible score on the DAST-20 questionnaire was 20, the mean reported scores for all patient groups were between only 1 and 3. There were no differences between MDD patients, BSD patients and controls on mean DAST-20 scores but BPAD patients had significantly higher scores than the three other groups ($F=9.41$, $df=3$, $p<0.01$).

Using the recommended threshold of 8 on the AUDIT screening questionnaire, 66% of all patients and 53% of controls screened positive for a possible alcohol use disorder. This difference was non-significant and there were no differences in positive screening rates between the MDD, BSD and BPAD groups. The mean AUDIT score was significantly higher in the BSD group compared to the MDD group ($t=-2.06$, $df=71$, $p<0.04$) and there was no difference between the BSD group and BPAD group on this measure.

Overall, as with drug use, levels of alcohol use during the preceding 12 months were lower than anticipated in all groups. This relatively low level of alcohol consumption may again be a consequence of under-reporting but, if we accept it as a true reflection of alcohol use in this sample, it may add strength to the neurocognitive findings presented in the next section, as heavy alcohol use has an obvious potential to confound neuropsychological studies.

b) Clinical course

There were also no significant differences between the three patient groups in terms of age at onset of depression or number of previous depressive episodes (table 2).

c) Family history

In terms of family history, there were very similar rates of at least one first degree relative with depression across all three patient groups (71.7% for MDD, 81.5% for BSD and 78.6% for BPAD). When the patient group as a whole was compared to controls, perhaps unsurprisingly, there was a significantly greater proportion of patients with a first degree relative with depression (X^2=13.8, df=1, p<0.001). A direct comparison between MDD patients and BSD patients on family history of depression was non-significant (table 2).

There were similar rates of having a first degree relative with bipolar disorder within the BSD and BPAD groups and no bipolar family history within the MDD or control groups. Rates of a bipolar family history in the MDD and BSD groups were significantly different (X^2=15.31, df=1, p<0.001), although clearly this may be related to the fact that having a first degree relative with bipolar disorder was one of the core diagnostic features of BSD. Having said this, it is still of interest that similar rates of family history for bipolar disorder were found in the BSD and BPAD probands (29.6% versus 21.4% respectively).

d) Treatment response

The only data that was collected that can be used to make an assessment of treatment response was the rate of antidepressant-associated hypomania. As with family history for bipolar disorder, this criterion was also a core diagnostic feature of BSD. Unsurprisingly, this too showed significantly different rates between the MDD and BSD groups (44.4% in the BSD group versus 0% in the MDD group; X^2=24.47, df=1, p<0.001). Rates of antidepressant-associated hypomania were very similar in the BSD and BPAD groups (44.4% and 42.9% respectively).

3.2 Neurocognitive function in young adults with MDD and BSD

The findings of the neuropsychological study are reported in this section. As noted in the methods chapter, 42 MDD patients and 21 BSD patients achieved euthymia (defined as at least one month of clinical remission with a score of less than 8 on the HRSD). These patients underwent neurocognitive testing along with 33 euthymic controls with no past history of mood disorder. The neuropsychological battery tested two principal cognitive domains: verbal memory and attention/executive function.

3.2.1 Baseline demographic and clinical characteristics compared

The three diagnostic groups were well matched in terms of age, gender distribution, handedness and current depressive symptoms (table 3). The estimate of premorbid intellectual function (that is, a combination of NART IQ score, block design score on the WAIS and number of years in education) was also similar across the three groups. There were no differences in these variables when the three groups were compared using ANOVA and a Tukey post hoc analysis did not identify differences between MDD patients versus BSD patients, BSD patients versus controls or MDD patients versus controls.

Table 3 also contains clinical data relating to the MDD and BSD groups, including mean age at onset of depression, mean number of depressive episodes and class of medication at the time of neuropsychological testing. A direct comparison between the MDD and BSD groups did not find any significant differences between them on these clinical variables, although the mean number of depressive episodes was approaching significance (BSD = 4.7, MDD = 4.0; $p<0.06$).

A chi-squared comparison of medication status in the MDD and BSD groups was also non-significant but this is potentially a complex area. Because of this, a more detailed table of medications being taken by patients in both groups is included in table 4. Inspection of this table reveals that more MDD patients were taking antidepressants alone compared to BSD patients (MDD = 83% versus BSD = 62%) and that a greater proportion of BSD patients were taking mood stabilisers alone (MDD = 10% versus BSD = 19%). BSD patients were also more frequently taking a mood stabiliser plus an antidepressant (MDD = 5% versus BSD = 19%). It might be argued that these differences (although non-significant on a straightforward chi-squared comparison) may represent potential confounding factors. In particular, the fact that more BSD patients were on combination therapy (a mood stabiliser plus an antidepressant) may be an important confound. This issue is considered in more detail within the discussion chapter.

The relative frequencies of each of the BSD criteria for the 21 BSD patients is presented in table 5. It is may be the case that the BSD criteria are not necessarily detecting bipolarity but rather are simply selecting out a more severe unipolar depressive sub-group, for example, young patients who have had psychotic episodes. If this were the case, then differences in performance on neuropsychological testing might simply be a consequence of a more severe depressive disorder in the BSD group. However, the figures in table 5 do not support this. None of the BSD patients who underwent neuropsychological testing had psychotic depression. This issue is also addressed in more detail within the discussion chapter.

Table 3. Demographic and clinical characteristics: MDD versus BSD versus Controls.

Characteristic	**MDD (n=42)** *Mean (SD)*	**BSD (n=21)** *Mean (SD)*	**Controls (n=33)** *Mean (SD)*	*ANOVA* **F** (df)	***P***	**MDD v BSD** (Tukey post hoc) ***P***	**BSD v Controls** (Tukey post hoc) ***P***	**MDD v Controls** (Tukey post hoc) ***P***
Age (years)	21.4 (1.91)	22.4 (2.75)	22.2 (2.29)	2.19 (2, 93)	0.12	0.18	0.95	0.22
NART IQ	117.8 (3.13)	117.1 (4.63)	115.9 (3.61)	2.40 (2, 93)	0.10	0.80	0.46	0.08
Block design (WAIS)	45.3 (6.67)	44.1 (4.27)	45.8 (3.13)	0.71 (2, 93)	0.71	0.93	0.52	0.64
Education (years)	16.6 (1.52)	16.9 (1.77)	17.3 (1.40)	2.10 (2, 93)	0.13	0.77	0.56	0.11
HRSD score	2.5 (1.90)	2.6 (2.09)	1.9 (0.93)	1.18 (2, 93)	0.31	0.93	0.35	0.44
Right-handed:left-handed	39:3	19:2	32:1	X^2=1.03 (df=2)	0.60	---	---	---
Gender ratio (F:M)	29:13	14:7	19:14	X^2=1.11 (df=2)	0.57	---	---	---
MDD versus BSD:				***MDD versus BSD:*** ***t* value (df)**				
Age at onset of depression	15.7 (2.61)	15.0 (2.77)	---	1.04 (1, 61)	0.31	---	---	---
No. depressive episodes	4.0 (1.46)	4.7 (1.42)	---	-1.9 (1, 61)	0.06	---	---	---
Current medications:								
Antidepressants only, n (%)	35 (83)	13 (62)	---	X^2=3.54 (df=1)	0.06	---	---	---
Mood stabilisers only, n (%)	4 (10)	4 (19)	---	X^2=1.15 (df=1)	0.29	---	---	---
Both, n (%)	2 (5)	4 (19)	---	X^2=3.32 (df=1)	0.07	---	---	---
Neither, n (%)	1 (2)	0 (0)	---	X^2=0.51 (df=1)	0.48	---	---	---

Table 4. Details of classes and daily doses of psychotropic medications being taken by patient groups at the time of neuropsychological testing.

Psychotropic class	MDD group (n=42)	BSD group (n=21)
Antidepressants alone	35 patients (83.3%): 22 patients (52.3%) were taking SSRIs: 11 on citalopram, 4 on paroxetine, 7 on fluoxetine. SSRI equivalent doses: 9 patients on 20mg, 10 on 40mg and 3 on 60mg. 6 patients (14.3%) were taking an SNRI (all venlafaxine): 2 on 150mg, 3 on 225mg and 1 on 300mg 5 patients (11.9%) were taking a NaSSA (all mirtazepine): 2 on 30mg an 3 on 45mg. 2 patients (4.8%) were taking a TCA (both amitriptylline): both at 200mg	13 patients (61.9%): 5 patients (23.8%) were taking SSRIs: 3 on citalopram, 2 on fluoxetine. SSRI equivalent doses: 2 patients on 20mg, 3 on 40mg. 6 patients (28.6%) were taking an SNRI (all venlafaxine): 3 on 150mg, 2 on 225mg and 1 on 300mg 1 patient (4.8%) was taking a NaSSA (mirtazepine) at 30mg. 1 patient taking a RIMA (moclobemide) at 450mg.
Mood stabilisers alone	4 patients (9.5%): one patient on carbamazepine 800mg, one on sodium valproate 1g and 2 on sodium valproate 800mg	4 patients (19.0%): one patient on lamotrigine 100mg, 2 patients on sodium valproate 600mg and 1 patient on sodium valproate 800mg.
Both antidepressants and mood stabilisers	2 patients (4.8%): one on sodium valproate 600mg plus paroxetine 20mg, one on sodium valproate 800mg plus paroxetine 20mg	4 patients (19.0%): 2 patients were taking mirtazepine 30mg plus lamotrigine 100mg and 2 patients were taking venlafaxine 150mg plus sodium valproate 800mg.
No medication	1 patient (2.4%)	None

Table 5. Relative frequencies of each BSD criterion for patients satisfying BSD diagnostic criteria (n=21).

BSD criterion		n (%)
A	At least one major depressive episode	21 (100)
B	No spontaneous DSM-IV hypomanic or manic episodes	21 (100)
C	Either of the following, plus at least two items from criterion D, or both of the following plus one item from criterion D:	
C1	First degree relative with bipolar disorder	6 (28.6)
C2	Antidepressant-induced mania or hypomania	11 (52.4)
D	If no items from criterion C are present, at least six of:	
D1	Hyperthymic personality (at baseline, non-depressed state)	7 (33.3)
D2	Recurrent major depressive episodes (> 3)	20 (95.2)
D3	Brief major depressive episodes (< 3 months)	21 (100)
D4	Atypical depressive symptoms (DSM-IV criteria)	6 (28.6)
D5	Psychotic major depressive episodes	0 (0)
D6	Early age of onset of major depressive episode (< age 25)	21 (100)
D7	Postpartum depression	0 (0)
D8	Antidepressant 'wear-off' (acute but not prophylactic response)	10 (47.6)
D9	Lack of response to > 2 antidepressant treatment trials	7 (33.3)

3.2.2 Neurocognitive function results

Table 6 contains the mean scores and standard deviations for each of the neuropsycholological tests that were administered to the three groups (MDD, BSD and controls). A mulitvariate analysis of variance (MANOVA) comparing these groups found significant differences between them within several of the CVLT categories, for the Stroop Colour Word test and for both parts of the Trail-making test (A and B) (table 6). With respect to the CVLT, the significant differences were identified in trials 1 to 5, trials 1 to 5 total free recall, short delay free recall, cued recall (C1.1, C1.4, C2.1, C2.4), long delay free recall and recognition. The differences between groups were non-significant for the Stroop Colour test and the Brixton Spatial Anticipation Test. From this analysis, MDD patients and BSD patients differed from controls on many of the tests of verbal learning and memory as well as on two of the three tests of attention and executive function. Furthermore, from inspection of the mean scores within table 6, it can be seen that the BSD patients consistently performed less well than the MDD patients on all of the tests.

Given that performance on these tests may be influenced by factors such as gender, age, premorbid IQ and current levels of depressive symptoms, these variables should be taken into account where possible (even though from, table 3, the three groups are reasonably well matched on these variables). To address this, another MANOVA was calculated with gender as a 'between subjects' factor and with age, premorbid IQ (NART score) and depressive symptoms (HRSD score) entered as covariates (table 7). It can be seen that this further MANOVA does not alter the main findings presented in table 6. All of the tests that were significantly different between groups from table 6 remain significantly different in table 7. This finding suggests

that the differences in performance were not confounded by subtle differences between groups on gender ratio, age, premorbid IQ or low levels of depressive symptoms at the time of testing.

In order to identify where the differences between groups lay, an ANOVA, with a post hoc Tukey HSD test, was carried out for those variables where a significant main effect was identified by MANOVA. This allowed a comparison to be made between MDD patients and BSD patients, between BSD patients and controls and between MDD patients and controls. These findings are presented in table 8.

i) MDD versus BSD:

On the CVLT, statistical differences between the MDD group and the BSD group emerged for trials 1 to 5 total free recall ($p<0.05$), short delay recall ($p<0.009$), cued recall (C1.1, C1.4, C2.1, C2.4; $p<0.05$ to $p<0.02$) and recognition hits ($p<0.02$).

For tests of attention and executive function, the only significant difference between the MDD and BSD groups was in the Trail-making test, part B ($p<0.03$).

ii) BSD versus controls:

BSD patients performed significantly less well than controls on all of the neuropsychological test scores outlined in table 8, with significance levels ranging from 0.001 to 0.04.

iii) MDD versus controls:

Differences were less pronounced when MDD patients were compared to controls. Although the mean scores for MDD patients were lower than controls for most of the

tests, only trials 4 and 5 of the CVLT ($p<0.05$) and Trail-making A ($p<0.001$) and B ($p<0.005$) were statistically significant (table 8).

Table 6. Neuropsychological test scores: MDD versus BSD versus Controls (MANOVA).

Neuropsychological domain and measure	MDD patients (n=42) *Mean (SD)*	BSD patients (n=21) *Mean (SD)*	Controls (n=33) *Mean (SD)*	*MANOVA* F (df=2, 93)	*P*
CVLT:					
Trial 1	7.2 (1.59)	6.4 (2.25)	7.7 (1.79)	3.37	0.04
Trial 2	10.7 (2.46)	9.8 (2.45)	11.8 (1.64)	5.48	0.006
Trial 3	12.2 (2.08)	11.0 (2.43)	13.1 (1.92)	6.15	0.003
Trial 4	13.1 (1.70)	12.3 (2.99)	14.2 (1.56)	6.22	0.003
Trial 5	13.6 (1.75)	12.9 (2.64)	14.7 (1.36)	6.09	0.003
Trials 1 to 5 total recall	56.8 (7.18)	52.0 (9.90)	60.7 (6.57)	8.49	0.001
List B recall	7.1 (1.98)	7.1 (2.56)	7.5 (1.75)	0.46	0.63
Short delay recall	13.1 (2.28)	11.2 (3.05)	13.5 (1.91)	6.38	0.003
C1.1	3.4 (0.89)	2.6 (1.02)	3.3 (0.76)	5.85	0.004
C1.2	3.3 (0.83)	3.1 (0.89)	3.3 (0.73)	0.45	0.64
C1.3	3.3 (0.78)	3.1 (0.73)	3.3 (0.74)	0.46	0.63
C1.4	3.6 (0.54)	3.0 (1.02)	3.6 (0.66)	6.85	0.002
Long delay recall	12.9 (2.45)	11.9 (2.89)	13.9 (1.98)	4.58	0.01
C2.1	3.5 (0.80)	2.7 (1.23)	3.4 (0.78)	5.47	0.006
C2.2	3.1 (0.74)	3.1 (0.81)	3.3 (0.73)	0.89	0.41
C2.3	3.4 (0.77)	3.2 (0.98)	3.5 (0.67)	1.10	0.39
C2.4	3.6 (0.54)	3.2 (1.03)	3.7 (0.54)	3.68	0.03
Recognition hits	15.0 (1.29)	14.0 (1.82)	15.2 (0.99)	5.60	0.005
Attention/executive function:					
Stroop colour	111.62 (0.58)	111.67 (0.73)	111.70 (0.47)	0.17	0.84
Stroop colour-word	109.52 (2.11)	108.29 (3.23)	110.42 (1.17)	6.29	0.003
Brixton test (raw score)	13.1 (4.12)	12.3 (3.69)	11.3 (4.10)	1.87	0.16
Trail-making Part A (s)	29.6 (7.83)	32.7 (7.93)	23.0 (4.83)	14.37	0.001
Trail-making Part B (s)	55.9 (15.13)	65.6 (16.57)	45.3 (10.88)	13.53	0.001

Table 7. Neuropsychological test scores: MANOVA with gender as a 'between subjects' factor and age, premorbid IQ and current symptoms as covariates.

Neuropsychological domain and measure	MDD patients (n=42) *Mean (SD)*	BSD patients (n=21) *Mean (SD)*	Controls (n=33) *Mean (SD)*	*MANOVA* F (df=2, 87)	*P*
CVLT:					
Trial 1	7.2 (1.59)	6.4 (2.25)	7.7 (1.79)	3.12	0.05
Trial 2	10.7 (2.46)	9.8 (2.45)	11.8 (1.64)	5.39	0.006
Trial 3	12.2 (2.08)	11.0 (2.43)	13.1 (1.92)	4.99	0.009
Trial 4	13.1 (1.70)	12.3 (2.99)	14.2 (1.56)	7.87	0.001
Trial 5	13.6 (1.75)	12.9 (2.64)	14.7 (1.36)	6.52	0.002
Trials 1 to 5 total recall	56.8 (7.18)	52.0 (9.90)	60.7 (6.57)	8.92	0.001
List B recall	7.1 (1.98)	7.1 (2.56)	7.5 (1.75)	0.49	0.61
Short delay recall	13.1 (2.28)	11.2 (3.05)	13.5 (1.91)	7.40	0.001
C1.1	3.4 (0.89)	2.6 (1.02)	3.3 (0.76)	4.97	0.009
C1.2	3.3 (0.83)	3.1 (0.89)	3.3 (0.73)	0.54	0.586
C1.3	3.3 (0.78)	3.1 (0.73)	3.3 (0.74)	1.04	0.357
C1.4	3.6 (0.54)	3.0 (1.02)	3.6 (0.66)	6.67	0.002
Long delay recall	12.9 (2.45)	11.9 (2.89)	13.9 (1.98)	5.80	0.004
C2.1	3.5 (0.80)	2.7 (1.23)	3.4 (0.78)	4.60	0.01
C2.2	3.1 (0.74)	3.1 (0.81)	3.3 (0.73)	1.49	0.23
C2.3	3.4 (0.77)	3.2 (0.98)	3.5 (0.67)	1.95	0.15
C2.4	3.6 (0.54)	3.2 (1.03)	3.7 (0.54)	4.66	0.01
Recognition hits	15.0 (1.29)	14.0 (1.82)	15.2 (0.99)	6.09	0.003
Attention/executive function:					
Stroop colour	111.62 (0.58)	111.67 (0.73)	111.70 (0.47)	1.33	0.27
Stroop colour-word	109.52 (2.11)	108.29 (3.23)	110.42 (1.17)	4.69	0.01
Brixton test (raw score)	13.1 (4.12)	12.3 (3.69)	11.3 (4.10)	1.73	0.183
Trail-making Part A (s)	29.6 (7.83)	32.7 (7.93)	23.0 (4.83)	15.00	0.001
Trail-making Part B (s)	55.9 (15.13)	65.6 (16.57)	45.3 (10.88)	12.28	0.001

Table 8. ANOVA with Tukey HSD post hoc test for neuropsychological tests demonstrating significant main effect from MANOVA.

Neuropsychological domain and measure	MDD patients (n=42)	BSD patients (n=21)	Controls (n=33)	*ANOVA*		MDD v BSD	BSD v Controls	MDD v Controls
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	**F** (df=2, 93)	***P***	***P***	***P***	***P***
CVLT:								
Trial 1	7.2 (1.59)	6.4 (2.25)	7.7 (1.79)	3.37	0.04	0.19	0.03	0.53
Trial 2	10.7 (2.46)	9.8 (2.45)	11.8 (1.64)	5.48	0.006	0.28	0.005	0.09
Trial 3	12.2 (2.08)	11.0 (2.43)	13.1 (1.92)	6.15	0.003	0.10	0.002	0.17
Trial 4	13.1 (1.70)	12.3 (2.99)	14.2 (1.56)	6.22	0.003	0.31	0.003	0.05
Trial 5	13.6 (1.75)	12.9 (2.64)	14.7 (1.36)	6.09	0.003	0.31	0.003	0.05
Trials 1 to 5 total recall	56.8 (7.18)	52.0 (9.90)	60.7 (6.57)	8.49	0.001	0.05	0.001	0.07
Short delay recall	13.1 (2.28)	11.2 (3.05)	13.5 (1.91)	6.34	0.003	0.009	0.003	0.84
C1.1	3.4 (0.89)	2.6 (1.02)	3.3 (0.76)	5.85	0.004	0.003	0.02	0.80
C1.4	3.6 (0.54)	3.0 (1.02)	3.6 (0.66)	6.85	0.002	0.002	0.006	0.96
Long delay recall	12.9 (2.45)	11.9 (2.89)	13.9 (1.98)	4.58	0.01	0.22	0.009	0.21
C2.1	3.5 (0.80)	2.7 (1.23)	3.4 (0.78)	5.47	0.006	0.005	0.03	0.80
C2.4	3.6 (0.54)	3.2 (1.03)	3.7 (0.54)	3.68	0.03	0.05	0.04	0.95
Recognition hits	15.0 (1.29)	14.0 (1.82)	15.2 (0.99)	5.60	0.005	0.02	0.004	0.68
Attention/executive function:								
Stroop colour-word	109.52 (2.11)	108.29 (3.23)	110.42 (1.17)	6.29	0.003	0.09	0.002	0.18
Trail-making Part A (s)	29.6 (7.83)	32.7 (7.93)	23.0 (4.83)	14.37	0.001	0.23	0.001	0.001
Trail-making Part B (s)	55.9 (15.13)	65.6 (16.57)	45.3 (10.88)	13.53	0.001	0.03	0.001	0.005

Although these differences identified between the three groups are of considerable interest, it should be acknowledged that they are still quite subtle and that many of the scores for the patient groups may fall within the normal range. Furthermore, these differences will not necessarily be associated with significant cognitive or functional impairment. In order to quantify the degree of difference in performance between the groups, effect sizes have been calculated and are presented in table 9. In table 10, the percentage of MDD and BSD patients falling below the 5th percentile of controls (for those scores that were identified as demonstrating a significant main effect from the MANOVA) are also presented. This latter measure quantifies how many of the MDD and BSD patients performed at a very low level relative to controls.

In terms of effect sizes, Cohen's convention suggests that less than 0.5 should be considered small, between 0.5 and 0.7 should be considered medium and more than 0.8 should be thought of as large [186]. When the MDD and BSD groups were compared to controls, most of the effect sizes were in the medium to large range (table 9). For example, for the CVLT category of trials 1 to 5 total free recall, the effect size for BSD patients versus controls was 1.04 and for MDD patients versus controls it was 0.57. Similarly, for the Trail-making test part B, the effect size for BSD patients versus controls was 1.45 and for MDD patients versus controls it was 0.76. These findings suggest that the differences between the two patient groups and controls were notable and it is of interest that the effect sizes for BSD patients versus controls were consistently higher than the effect sizes for MDD patients versus controls.

In terms of the comparison between the MDD group and the BSD group, most of the effect sizes lay within the medium range (eg, CVLT trials 1 to 5 total free recall

= 0.56, CVLT short delay recall = 0.71, CVLT recognition hits 0.63 and Trail-making part B = 0.61). This suggests that although the differences between the BSD group and the MDD group were smaller than between either of these groups and controls, they were still important.

This is supported by the data in table 10 showing the percentage of MDD and BSD patients scoring below the 5th percentile of controls. It is notable that 38% of BSD patients and 17% of MDD patients were below the 5th percentile of controls for the CVLT trails 1 to 5 total free recall and that the corresponding figures for the CVLT short delay recall were 33% of BSD patients and 14% of MDD patients. These findings were even more pronounced for the tests of attention and executive function. Forty seven percent of BSD patients (and 28% of MDD patients) were below the 5th percentile for the Stroop Colour Word test. Similarly, 71% of BSD patients and 45% of MDD patients were below the 5th percentile for the Trail-making test part A. The figures for Trail-making part B were 52% of BSD patients and 21% of MDD patients.

Table 9. Effect sizes for neuropsychological tests demonstrating significant main effect from MANOVA.

Neuropsychological domain and measure	Effect size: *MDD v BSD*	Effect size: *BSD v Controls*	Effect size: *MDD v Controls*
CVLT:			
Trial 1	0.41	0.64	0.30
Trial 2	0.37	0.96	0.53
Trial 3	0.53	0.96	0.40
Trial 4	0.33	0.80	0.67
Trial 5	0.08	0.86	0.70
Trials 1 to 5 total recall	0.56	1.04	0.57
Short delay recall	0.71	0.90	0.15
C1.1	0.84	0.78	0.12
C1.4	0.74	0.70	0
Long delay recall	0.37	0.81	0.45
C2.1	0.77	0.68	0.13
C2.4	0.49	0.61	0.19
Recognition hits	0.63	0.82	0.17
Attention/executive function:			
Stroop colour-word	0.45	0.88	0.53
Trail-making Part A (s)	0.39	1.48	1.01
Trail-making Part B (s)	0.61	1.45	0.76

Table 10. Percentage of MDD and BSD patients scoring below the 5th percentile of controls (for tests demonstrating significant main effect from MANOVA).

Neuropsychological test	MDD patients below the 5th percentile of controls n (%)	BSD patients below the 5th percentile of controls n (%)
CVLT:		
Trial 1	1 (2.4)	3 (14.3)
Trial 2	13 (31.0)	10 (47.6)
Trial 3	5 (11.9)	5 (23.8)
Trial 4	6 (14.3)	8 (38.1)
Trial 5	12 (28.6)	8 (38.1)
Trials 1 to 5 total recall	7 (16.7)	8 (38.1)
Short delay recall	6 (14.3)	7 (33.3)
C1.1	7 (16.7)	8 (38.1)
C1.4	1 (2.4)	6 (28.6)
Long delay recall	8 (19.0)	7 (33.3)
C2.1	6 (14.3)	8 (38.1)
C2.4	1 (2.4)	4 (19.0)
Recognition hits	8 (19.0)	6 (28.6)
Attention and executive function:		
Stroop colour-word	12 (28.6)	10 (47.6)
Trail-making Part A (s)	19 (45.2)	15 (71.4)
Trail-making Part B (s)	9 (21.4)	11 (52.4)

3.2.3 Correlations between illness characteristics and neurocognitive performance

Tables 11 and 12 present the findings of a correlation analysis between illness characteristics (age at illness onset and number of previous depressive episodes) and performance on neuropsychological testing. No significant correlation was detected between number of depressive episodes and cognitive performance for either of the two patient groups.

However, age at onset was negatively correlated with some of the CVLT test scores for both the MDD patients and the BSD patients. In the MDD group (table 11), there was a significant negative correlation between age at onset and CVLT trial 3 ($p<0.05$), trial 4 ($p<0.007$) and trials 1 to 5 total free recall ($p<0.05$). For the BSD group (table 12) a significant negative correlation between age at onset and performance was found for two of the cued recall scores (C1.4, $p<0.02$ and C2.4, $p<0.03$). It is interesting that none of the attention or executive function tests showed any correlation with age at onset or number of depressive episodes for either of the patient groups.

To summarize, these findings suggest that early age at onset in MDD, and, to a lesser extent, in BSD, is associated with poorer performance on certain tests of verbal memory but not associated with impaired attentional or executive function. Further, there was no association for either patient group between verbal memory or attention/executive function performance and number of previous depressive episodes. One conclusion from this might be that verbal memory impairment in MDD and BSD is more closely related to early age at onset (and possibly, by extension, either greater genetic loading for affective disorder or the experience of

more adverse events in childhood) rather than simply being a consequence of recurrent episodes of illness. This finding is considered in more detail within the discussion section.

Table 11. Correlations between illness characteristics and neuropsychological performance (MDD patients, n=46).

Neuropsychological test	Age at onset Pearson's *r*, *P*	Number of depressive episodes Pearson's *r*, *P*
CVLT:		
Trial 1	-0.16, 0.31	0, 1
Trial 2	-0.12, 0.45	-0.10, 0.54
Trial 3	**-0.31, 0.05**	0.03, 0.87
Trial 4	**-0.41, 0.007**	0.17, 0.29
Trial 5	-0.18, 0.25	-0.12, 0.46
Trials 1 to 5 total recall	**-0.31, 0.05**	-0.04, 0.82
Short delay recall	-0.22, 0.16	0.01, 0.96
C1.1	0.14, 0.37	-0.11, 0.51
C1.4	-0.09, 0.57	-0.14, 0.39
Long delay recall	-0.16, 0.33	0.01, 0.93
C2.1	0.11, 0.49	-0.14, 0.39
C2.4	-0.17, 0.20	-0.10, 0.45
Recognition hits	0.05, 0.73	-0.18, 0.25
Attention and executive function:		
Stroop colour-word	-0.04, 0.80	-0.14, 0.38
Trail-making Part A (s)	0.03, 0.87	0.01, 0.97
Trail-making Part B (s)	0.03, 0.87	0.05, 0.77

Table 12. Correlations between illness characteristics and neuropsychological performance (BSD patients, n=21).

Neuropsychological test	Age at onset Pearson's *r*, *P*	Number of depressive episodes Pearson's *r*, *P*
CVLT:		
Trial 1	-0.03, 0.89	0.83, 0.72
Trial 2	0.03, 0.90	0.07, 0.78
Trial 3	-0.15, 0.52	0.17, 0.45
Trial 4	-0.11, 0.64	0.02, 0.92
Trial 5	-0.34, 0.13	0.25, 0.28
Trials 1 to 5 total recall	-0.18, 0.44	0.11, 0.64
Short delay recall	-0.33, 0.14	0.35, 0.12
C1.1	-0.12, 0.60	0.09, 0.69
C1.4	**-0.49, 0.02**	0.40, 0.07
Long delay recall	-0.34, 0.13	0.30, 0.20
C2.1	-0.06, 0.80	0.04, 0.87
C2.4	**-0.47, 0.03**	0.24, 0.29
Recognition hits	-0.17, 0.47	0.29, 0.20
Attention and executive function:		
Stroop colour-word	0.05, 0.85	-0.04, 0.88
Trail-making Part A (s)	0.14, 0.56	-0.17, 0.47
Trail-making Part B (s)	0.03, 0.91	-0.33, 0.89

Chapter 4 Discussion

4.1 Diagnostic and clinical findings

4.1.1 Discussion of diagnostic and clinical findings

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4.2.3 Future directions

4.1 Diagnostic and clinical findings

4.1.1 Discussion of diagnostic and clinical findings

In the introduction to this thesis I have presented data that suggests that an onset of major depression in adolescence or young adulthood, that is followed by recurrence of depression, may represent a precursor for the development of bipolar disorder. Unlike unipolar depression, which tends to begin later in life, bipolar disorders characteristically begin (usually with a depressive episode) in adolescence or early adulthood. It is also the case that there is often a long delay between the first presentation of a bipolar disorder and diagnosis. Earlier detection of bipolar disorders therefore has the potential to impact significantly on future illness course.

I have reviewed evidence to suggest that ICD-10 and DSM-IV (by virtue of having broad criteria for depression but relatively narrow criteria for bipolar disorder) have tended to over-diagnose recurrent depressive disorder at the expense of bipolar disorders. This observation has led to the suggestion of modifications to the DSM-IV criteria, such as including behavioural activation as a stem criterion and reducing the minimum duration threshold for hypomanic symptoms from 4 to 2 days [73]. It has also led to the suggestion of structured diagnostic criteria for bipolar spectrum disorder (BSD) [93] (figure 10) that highlight the importance of factors such as having a first degree family history of bipolar disorder or a personal history of antidepressant-associated hypomania.

When one considers that young adults with early-onset, recurrent depression may be at high risk of ultimately developing a bipolar disorder throughout their lifetime, it is perhaps not surprising that many of the patients in this study satisfied

the BSD criteria for a 'softer', or more broadly-defined, bipolar disorder. Out of the 73 patients with recurrent MDD, 27 (37%) also fulfilled the BSD criteria. Nineteen of these 27 patients (70%) had at least one of the core BSD criteria (either a positive first degree family history of bipolar disorder or a personal history of antidepressant-associated hypomania). Including those 14 patients from the cohort with BPAD means that 41 (47%) of these consecutively-recruited patients could be considered to have a broadly defined bipolar illness. This figure is in line with the 1:1 ratio of broadly-defined bipolar disorder to depression identified in the Zurich study [75, 188] and in a number of other studies [77, 79, 189, 190]. In clinical practice, this would suggest that young adults with early-onset, recurrent depression should be carefully assessed for the possibility that they might have an early bipolar disorder.

Diagnosing a possible bipolar disorder rather than a straightforward unipolar disorder may have important implications for the pharmacological treatment choices that are made. It appears to be the case that a significant proportion of bipolar patients (around 20%) may be ill-served by recurrent courses of antidepressant medication that can cause anti-depressant associated hypomania, mixed affective states and a rapid-cycling course of illness [86].

4.1.2 Limitations of diagnostic findings

Although the first main finding in this thesis was the relatively high number of young patients who satisfied the criteria for BSD, the relevance and importance of this finding depends on a number of factors. It must be acknowledged that the criteria for BSD are not yet fully validated in large patient samples. There is good evidence that the two core criteria in BSD are associated with bipolar disorder (that is, having recurrent depression with either a first degree relative with bipolar disorder or a personal history of antidepressant-associated hypomania). Both of these factors have been identified as predicting bipolar outcome in several longitudinal studies of depressed patients [85, 86, 88, 89, 188]. However, the evidence for the 9 additional clinical features also outlined in the BSD criteria as being strongly associated with bipolar outcome is somewhat less convincing. Indeed, the threshold of 6 out of these 9 features required to be present in the absence of the 2 core criteria appears to have been an arbitrary choice with no clear justification. A further criticism might be that the assessment of these 'soft bipolar' features at a single interview and without corroborative information from family members is unreliable. Having said this, as noted above, the majority of BSD patients in this study (70%) were diagnosed as having BSD on the basis of at least one of the core diagnostic features rather than on the basis of the secondary (and probably less reliable) criteria, adding strength to the assertion that they may have a bipolar-related illness.

At the time of writing there has been only one published study which has directly assessed the validity of the BSD criteria against DSM-IV diagnosed BPAD patients. Ghaemi and colleagues compared 36 patients with DSM-IV bipolar I or II disorder to 37 unipolar depressives [92]. The five most powerful predictors of bipolar

disorder were brief major depressive episodes, early age at onset, anti-depressant associated hypomania, postpartum depression and atypical depressive symptoms. Perhaps surprisingly, family history for bipolar disorder did not emerge in this study as a major predictor for bipolar disorder.

4.1.3 Can the BSD criteria be validated in this sample according to clinical parameters?

Because of the small numbers of BPAD patients (n=14) relative to MDD (n=46) and BSD (n=27) patients assessed at the beginning of the current study, it is difficult to draw firm conclusions about the validity of the BSD criteria based on comparisons of clinical features between the three diagnostic groups. Despite this, some of the clinical data collected permit a preliminary consideration of the validity of the BSD criteria by assessing similarities and differences between these groups. As noted in the introduction, the classic Robins and Guze criteria for validating the diagnosis of a psychiatric disorder include: *i)* clinical phenomenology; *ii)* clinical course; *iii)* family history; and *iv)* treatment response [166].

In terms of clinical phenomenology, it might be argued that the higher rate of atypical depression in the BSD group compared to the MDD group (26% versus 9%) is suggestive of a bipolar-type disorder because atypical depression appears to be more common in bipolar depressive episodes (and especially those with bipolar II disorder) compared to unipolar episodes [59, 60, 92]. It has also been shown that patients with atypical depression have relatively high rates of soft bipolar features [187]. However, it is also the case that only one of the 14 BPAD patients in this data set (7%) had atypical depression. Clearly this analysis would have benefited from comparison with a larger number of DSM-IV BPAD patients.

The clinical course of the three diagnostic groups was very similar in terms of age at onset of depression and number of previous depressive episodes. From what is already known about the natural history of unipolar depression and bipolar disorder, it might have been expected that the BPAD and BSD groups would have had an earlier

age at onset and more depressive episodes. Although the BSD patients were no different from the MDD patients on number of previous depressive episodes, this may have been because only a relatively brief period had passed (approximately 7 years) since their first episode. A longer period of follow up might be expected to show more episodes for the BSD and BPAD groups relative to the MDD group.

Similarly, the BSD patients did not differ significantly from the MDD patients (and were not necessarily more closely similar to the BPAD patients) on clinical course features such as a history of deliberate self-harm, previous suicide attempts, DAST-20 scores or AUDIT scores. It may be of interest that for rates of a history of deliberate self-harm and in terms of raw DAST-20 scores the BSD patients appeared to occupy an intermediate position between the MDD patients and BPAD patients (table 2). It would be difficult to argue, however, that this represented good evidence for the validity of the BSD criteria based on clinical course features, especially when a direct comparison between BSD patients and MDD patients on these variables does not identify any significant differences (table 3).

Any attempt to validate the BSD criteria on the basis of family history is likely to be difficult because family history for bipolar disorder was one of the core criteria for BSD. Nonetheless, it is interesting that the rate of bipolar family history was similar in the BSD and BPAD groups (30% versus 21% respectively). Although the rates of having at least one first degree relative with depression were 72% in the MDD group, 82% in the BSD group and 79% in the BPAD group, these differences were not statistically significant. It might have been expected that the BSD criteria would identify higher rates of depression in the BSD and BPAD groups but this is not the case. Overall, family history in this data set does not provide any substantial support for the validity of the BSD criteria.

It is also difficult to apply Robins and Guzes' final validity criterion, treatment response, to these data because this was not formally assessed apart from the information that was gathered on a past history of antidepressant-associated hypomania. As with having at least one first degree relative with bipolar disorder, this variable was a core feature of the BSD criteria. As a result, it probably should not be used to formally assess the validity of the BSD criteria. From a purely clinical perspective, however, it is of interest that 44% of BSD patients and 43% of BPAD patients had experienced antidepressant-associated hypomania.

Overall, the clinical data permit only a cautious assessment of the validity of the BSD criteria. It would appear that applying the Robins and Guze criteria for the validity of psychiatric diagnoses does not provide convincing evidence that the BSD criteria are valid in identifying bipolar disorder in this data set. This is the case even though some of the findings (such as the rates of atypical depression, the levels of family history for bipolar disorder and the rates of antidepressant-associated hypomania) might suggest that the BSD criteria may have some clinical usefulness.

4.1.4 Implications for the design of future studies assessing the validity of the BSD criteria

It is clear from the above that there were limitations to the degree to which clinical features could be used in this data set to make judgements about the validity of the BSD criteria. Not enough BPAD patients were available to make reliable comparisons between the groups, one of the validity criteria (treatment response) was not systematically assessed in sufficient detail and the group itself (mostly students) were highly selected in terms of social, economic and educational status. Having said this, there are very few studies of this kind published to date and these data represent one of the first attempts to report the clinical features of possible 'soft bipolar' disorders in a consecutively recruited cohort of young adults with recurrent MDD.

Ideally, future studies that are designed to assess the validity of the BSD criteria should identify large, socially and economically diverse cohorts of adolescents and young adults presenting with a first episode of major depression. They should be followed prospectively over a number of years (probably at least 20, so that they pass through the median age of onset of mania) and assessed on a regular basis according ICD-10, DSM-IV and BSD criteria. Information about clinical phenomenology, clinical course, family history and treatment response should be collected so that at the end of the study the Robins and Guze criteria can be applied.

This kind of study would be likely to generate a great deal of useful information about the correct diagnosis and clinical course of bipolar spectrum disorders but would obviously also be logistically difficult and extremely expensive. Nonetheless, this is exactly the kind of approach that was taken with the Zurich study which is now producing a great deal of useful information about the natural history of

mood disorders. A study of this length should also have the capacity to respond to changes in diagnostic practices. For example, it may be that subsequent versions of ICD and DSM will incorporate the idea that mood disorders should be diagnosed along a continuum rather than categorically.

A less ambitious, but perhaps more achievable, assessment of the validity of the BSD criteria could be achieved by applying the criteria to socially and demographically matched samples of patients with major depressive disorder and bipolar disorder. As with the preliminary study above by Ghaemi and colleagues, this approach may be able to identify which of the BSD criteria are most strongly associated with bipolar disorder rather than with major depressive disorder.

4.2 Neurocognitive findings

4.2.1 Discussion of neurocognitive findings

The aim of the neuropsychological study in this thesis was to compare neurocognitive function in the euthymic state between young adults with MDD, young adults with BSD and well matched euthymic controls. The main hypothesis being tested was that there would be differences between both of the patient groups and controls on tests of prefrontal and hippocampal function. Based on previous work of this kind with euthymic BPAD patients, it was also hypothesised that the BSD group might have a different pattern of cognitive performance than the MDD group.

From the neuropsychological literature of mood disorders, it appears to be the case that the patterns of neurocognitive impairment in euthymic BPAD patients, especially in the domains of attention/executive function and declarative memory, are similar to (but more severe than) those impairments that are seen in euthymic MDD patients. However, it should be remembered that at the time of writing there are no good quality studies published that directly compare euthymic bipolar patients to well matched euthymic unipolar patients. The greater degree of attention/executive function and declarative memory impairment in bipolar disorder relative to unipolar disorder may be a reflection of a number of factors. It is possible that it is a consequence of more severe affective episodes, more frequent episodes or greater life-long sub-syndromal psychopathology in bipolar patients. It may also be a result of a greater medication load or higher rates of drug and alcohol misuse in bipolar patients. Having said this, there is now evidence to suggest that although these factors do exert an influence on cognitive performance, they may not be as important as high genetic

loading for mood disorder. As discussed in the introduction, several studies have now suggested that impaired attention/executive function and/or declarative memory function in recovered patients with mood disorders may represent endophenotypic abnormalities, or intermediate phenotypes, that are closely linked to genetic risk. These suggestions come from twin and family studies [136, 137], retrospective and prospective analyses of premorbid neurodevelopmental functioning [139-141] and the assessment of unaffected biological relatives [142-144].

If one accepts that attentional abnormalities, executive dysfunction and/or declarative memory disturbances are indeed neurocognitive markers of a bipolar diathesis, then it would follow that young adult patients with a soft bipolar disorder might exhibit these abnormalities to a greater extent than MDD young adults or controls. Furthermore, if the suggested criteria for BSD used in this study are indeed defining a *bona fide* bipolar sub-group, it would be expected that there would be a gradation of deficit whereby BSD patients were most impaired, followed by MDD patients, followed by controls - this is in fact the pattern of neurocognitive impairment that has emerged in the present study.

To summarize the neurocognitive findings, there were significant differences between the BSD and MDD groups on several components of the CVLT (trials 1 to 5 total free recall, short delay recall, cued recall and recognition hits) and on the Trail-making test part B, suggesting that the BSD group were more impaired on both verbal memory and on one of the tests of executive function. Although the MDD group was more impaired than controls on some of the CVLT components (learning trials 3 and 4 and trials 1 to 5 total free recall) and on both part A and part B of the Trail-making test, the BSD group were much more impaired than controls on all of the CVLT components, on the Stroop Colour Word Test and on both parts of the Trail-making

test. These findings suggest that the range and degree of prefrontal and hippocampal impairment in euthymic BSD patients was greater than euthymic MDD patients and considerably greater than in controls. This pattern of both prefrontal and hippocampal impairment is consistent with a number of previous neuropsychological studies of bipolar disorder [101, 131-134, 191]. It is notable that this young euthymic patient group were selected for early age at onset and recurrence and that almost all had strong family histories of mood disorder. In this context, the finding of a combined deficit in prefrontal and hippocampal function supports the view that these impairments may represent endophenotypic traits that are markers of genetic vulnerability to bipolar disorder.

Given the age of this patient sample and the relatively high degree of matching in terms of baseline characteristics and previous illness course, these findings support the assertion that the BSD criteria are detecting a sub-group of young mood disordered patients with a strong bipolar diathesis which is a consequence of a higher genetic loading for mood disorder. Indirectly, these findings might also lend support to the validity of the BSD criteria. It could be argued, however, that as long as the exact pathophysiology of mood disorders remains unknown, diagnostic validity should only be assessed using the four clinical categories described by Robins and Guze.

It could be that the BSD criteria were simply detecting young patients with more severe unipolar depression (for example, with a past history of psychosis or more frequent depressive episodes) rather than necessarily picking up on a 'soft bipolar' phenotype. However, this does not appear to have been the case. None of the BSD patients in this study who underwent neuropsychological testing had a past history of psychotic symptoms and the BSD and MDD groups were well matched in

terms of age at onset, number of depressive episodes and severity of the most recent episode.

4.2.2 Limitations of neurcognitive findings

Although there were methodological strengths to this study, such as the use of objective structured diagnostic instruments and a high degree of matching between BSD patients, MDD patients and controls, there were also potential limitations that are addressed in more detail under the categories below.

a) How well were the groups matched on baseline characteristics?

Overall, compared to many previous studies of this kind, the patients and controls in this study were relatively homogeneous in terms of age, gender distribution, social class, educational status and estimates of premorbid IQ. There were no differences between the three groups on any of these variables. The two patient groups were also reasonably well matched in terms of levels of current symptoms and other clinical variables such as age at onset of depression, number of previous depressive episodes and current medications. Despite this relatively high degree of matching for baseline characteristics, the MANOVA presented in table 7, which compares BSD, MDD and controls on neuropsychological test scores, included an additional analysis of gender as a 'between subjects' factor and age, premorbid IQ (NART IQ score) and HRSD score entered as covariates. As noted in the results section, this additional analysis did not change any of the significant findings between groups.

A major limitation in the baseline data was the lack of an objective rating for current manic symptoms, such as the Young Mania Rating Scale (YMRS) [192]. A

measure such as this would be obligatory for any neuropsychological study involving DSM-IV bipolar patients, especially when being assessed during a period of clinical remission. Unfortunately, at the beginning of this study it had been decided that YMRS scores would not be collected as all of the patients tested had DSM-IV recurrent MDD. However, with hindsight and given that 11 out of the 21 BSD patients were subsequently found to have a past history of antidepressant-associated hypomania, not including a measure of current manic symptoms in the test battery was regrettable. None of the patients tested gave a history of recent hypomanic symptoms or, on clinical assessment, appeared to have hypomanic symptoms during testing. It is expected therefore that the effect of hypomanic symptoms at the time of testing was not significant.

A related issue is the way in which control subjects were recruited. This was done by asking patients enrolled in the study to volunteer a close friend, with no history of depression, to take part. It may be that this method of recruitment introduced a potential sampling bias in the sense that the controls may have been more curious than the broader population to become involved in a study that involved a psychiatric assessment and neuropsychological testing. In other words, the controls may have been particularly interested in mental health issues or psychology with the result that this could have biased some of their responses or made them more likely to perform better on the neuropsychological tests than general population controls.

b) What was the contribution of current medication to neuropsychological performance?

As outlined in table 4, there may have been subtle differences between the BSD patients and MDD patients in terms of medication at the time of testing (even though a chi-squared analysis of classes of psychotropics was non-significant, table 3). In general terms there were no large differences between the two groups in terms of levels of antidepressant use but it must be acknowledged that one of the 42 MDD patients was on no medication whereas all 21 of the BSD patients were on some kind of psychotropic. Furthermore, 19% of the BSD patients were on combined therapy (an antidepressant plus a mood stabiliser) compared to only 5% of the MDD patients. Although the literature suggests that subtle cognitive impairments are most likely to occur with traditional antipsychotic medications such as chlorpromazine, benzodiazepines, lithium and anticholinergic antidepressants such as tricyclics [129, 146-148], the effect of combination therapy is unknown. It must be acknowledged that some of the cognitive impairment observed in the BSD group may have been caused by the higher rate of combination therapy in this group.

c) How significant was the difference in neurocognitive performance between BSD patients, MDD patients and controls?

Several previous neuropsychological studies of mood-disordered patients have detected subtle differences in cognitive performance between patients and controls that do not necessarily extrapolate to functional impairments. The performance of BSD and MDD patients in this study on many of the tests, by virtue of their high premorbid levels of intellectual functioning, was relatively high and perhaps much higher than would be expected for a population not selected from a University clinic.

For this reason, it was important to calculate effect sizes for differences in performance between the groups, as well as estimating how many of the BSD and MDD patients fell below the 5th percentile of controls. The greatest effect sizes were seen in the comparison of BSD patients with controls (which were generally in the 'large' range, defined as effect size greater than 0.8). Comparing BSD patients with MDD patients produced effect sizes in the medium range (from 0.5 to 0.8) and comparing MDD patients with controls produced both medium and low effect sizes (less than 0.5).

Compared to other studies of this kind, these effect sizes are of a greater magnitude that perhaps might have been expected. For example, in a comparison of 63 euthymic BPAD patients and controls, Thompson and colleagues calculated effect sizes of 0.6 for the Stroop Colour Word Test, 0.6 for the RAVLT trials 1 to 5 total free recall and 0.2 for the Trail-making test part B [134]. The respective effect sizes in the current study were 0.9 for the Stroop Colour Word, 1.0 for the CVLT trials 1 to 5 total free recall and 1.5 for the Trail-making test part B. Although there were methodological differences between these two studies that may explain these differences, the effect sizes reported in this thesis suggest that the differences found between BSD patients and controls and BSD patients and MDD patients were important.

This is supported by the calculations of how many BSD and MDD patients fell below the 5th percentile of controls (table 10). It is striking that 71% of BSD patients were below the 5th percentile of controls for the Trail-making test part A and that the corresponding proportions for the Trail-making part B, Stroop Colour Word and CVLT trials 1 to 5 total free recall were 52%, 48% and 38% respectively. For the MDD patients, the corresponding figures were 45%, 21%, 29% and 17% respectively.

d) How significant were the correlations between illness characteristics and neurocognitive performance?

The calculation of correlations between age at onset and number of previous depressive episodes with neurocognitive function in the MDD and BSD groups was an exploratory exercise.

For both patient groups there were no significant correlations between number of depressive episodes and any of the tests. However, in the MDD group, trails 1 to 5 total free recall and two of the five initial learning trials (trials 3 and 4) were significantly negatively correlated with age at onset. Although this might suggest that earlier age at onset of MDD is associated with greater impairment of verbal learning and memory in the MDD group, the size of these correlations were relatively modest. If the association between age at onset and verbal memory were more substantial it might have been expected that several more of the CVLT categories would have been significant. The same applies to the BSD group, where only two of the CVLT categories (both in cued recall) were significantly negatively correlated with age at onset. There was no correlation in either group between age at onset and attention/executive performance.

To summarise these findings, it appears that overall there were no strong correlations in either patient group between age at onset or number of previous depressive episodes and neurocognitive performance. However, there were weak negative correlations between age at onset and verbal memory performance in both the BSD and MDD groups that were more pronounced in the MDD group. One possible explanation for this might be that hippocampal function in both patient groups is more strongly influenced by earlier onset of illness than the experience of repeated episodes of depression. This might suggest that hippocampal function in

these young patients is more closely related to higher genetic loading for mood disorder (which might cause an earlier age at onset) rather then the neurotoxic effect of repeated episodes. Although interesting, this is obviously a tentative suggestion because the correlations observed were so weak. Furthermore, it might have been expected that the BSD group correlations would be stronger than the MDD group correlations because the former would have been expected to have a higher genetic loading for mood disorder.

e) Can these findings be generalised to other populations?

As noted above, this sample of patients and controls were highly selected and may be unrepresentative of the general population. All were recruited from a University Health Service, most were either undergraduate or postgraduate students, the social class distribution was relatively high and there were lower than expected rates of drug and alcohol misuse. These represent limitations in terms of the degree to which the findings of this study can be generalised to broader patient populations. This applies particularly to the diagnostic findings. There have been reports that bipolar disorder is associated with higher social class [193], greater social achievement in first degree relatives [194] and greater premorbid educational achievement [195].

However, it might be argued that the homogeneity of the patient and control samples represent a strength of the neuropsychological study in the sense that both groups were young, they appeared to have low rates of substance misuse and, by virtue of coming from families of higher social class, may have been more likely than other samples to be free from major traumatic events in childhood (although this latter point is presumed and was not formally assessed).

f) Were the definitions of 'clinical remission' and 'euthymia' sufficiently rigorous?

It might be argued that a monthly clinical assessment of clinical remission and a HRSD of less than 8 were inadequate to be clear about euthymia (even though this definition is more stringent than that used in many previously published reports). It has been suggested that serial, and if possible daily, objective and subjective measurements of mood over at least a month and preferably over 3 months are necessary to establish euthymia with a high degree of certainty [134, 196].

Although it is possible that some of the patients assessed in the current study were not fully recovered for a sufficiently long time to be clear that they were clinically euthymic, as noted above, an additional analysis that took into account current HRSD scores was conducted (table 7). This did not influence the neurocognitive findings or the levels of significance. Given also that the raw HRSD scores for the three groups were not significantly different from each other, it is reasonable to suggest that residual depressive symptoms in this data set did not significantly confound the main findings.

4.2.3 Future directions

It seems possible that one of the explanations for the large number of studies carried out to date on the neuropsychology of mood disorders is the relative ease with which these studies can be conducted (compared, for example, to structural or functional imaging studies). On their own, neuropsychological studies are only able to point to potential abnormalities within putative neural circuits of mood disorder. The incorporation of structural and functional imaging data into studies of neurocognitive function will be necessary to visualise abnormalities of these circuits.

From a review of the literature, it is clear there remains a need for carefully designed studies that compare well matched samples of bipolar patients with unipolar patients and controls. This kind of comparison may help to clarify whether the neuropsychological profile of euthymic bipolar disorder is different from that of euthymic recurrent unipolar depression. Ideally, such studies should be able to take into account factors such as age at onset, number and severity of mood episodes, family history for mood disorder, current mood symptoms and the effects of past and current medications. In this regard, a prospective design (rather than a cross-sectional comparison) would be preferred as this would be able to separate out the effects of vulnerability from scarring and state effects.

One suggestion might be to recruit a cohort of medication-naïve adolescents with major depression and carry out serial neuropsychological assessments over a number of years (both during mood episodes and at times of rigorously-defined remission). From what is known from previous long-term follow-up studies, a proportion of these patients (perhaps up to 20%) would be expected to go on to develop a bipolar disorder during an assessment period of 20 years. Comparison of

bipolar patients and unipolar patients during this time period, taking into account the effects of illness course and medication, may be useful in helping to define the neuropsychological profile of bipolar disorder and recurrent unipolar depression.

Although an ambitious undertaking, the usefulness of this kind of study would be greatly enhanced by incorporating the examination of genetic risk factors and putative endophenotypic measures (such as HPA axis function or personality dimensions). It is likely that there is a complex relationship between genetic risk, neuroendocrine function, neurocognitive function, personality and the unipolar or bipolar phenotype. It could be argued that neuropsychological studies of mood disordered patients are only useful if the effects of genetic risk factors and neuroendocrine function are part of the study design. For example, it is known that abnormalities of some of the candidate genes for mood disorder, such as brain derived neurotrophic factor (BDNF), have important effects on cognition in both patients with mood disorder and controls [197-199]. Although it can be seen that this field is likely to progress by the integration of several different experimental approaches, it must be acknowledged that the execution of these studies is likely to be expensive and logistically difficult.

A key question for the future is whether bipolar patients are different from unipolar patients in terms of abnormalities of neural circuitry (detected through neuropsychological study and/or imaging), or whether bipolar illness is simply the expression a more severe form of unipolar disorder that arises as a consequence of higher genetic loading. This issue is important not only because of the implications for classification and diagnosis but also because it is likely to impact on treatment choices for patients presenting with recurrent episodes of depression. It remains to be

seen over the next few years whether the concept of a broadened bipolar spectrum is more widely accepted in clinical practice.

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Appendix

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CONSENT FORM
Version 1/2002

EDINBURGH DEPRESSION STUDY

Professor Douglas Blackwood, Dr Walter Muir, Dr Daniel Smith

I voluntarily agree to participate in this study that has been explained to me by Dr .....

- I have read the attached information sheet entitled Edinburgh Depression Study (version 1/2002) and have been given a copy to keep. I have been given the opportunity to ask questions about the project and understand why the research is being done.

- I understand that my general practitioner will be informed of my participation in the study. I give my permission for my medical notes to be looked at and information taken from them to be analysed in strict confidence by Professor Blackwood and Dr Muir's team.

- I understand that I have the right to withdraw from the study without giving a reason and without my medical treatment or legal rights being affected. I understand that the results of these investigations are unlikely to have any implications for me personally.

- I understand that I am under no obligation to take part in this study and a decision not to participate will not alter the treatment I receive. I know how to contact the research team if I need to.

.....	.....	.....
Name of subject (block letters)	Date	Signature
.....	.....	.....
Name of person taking consent	Date	Signature

Assessment instruments used in this study

Drug Use Questionnaire (DAST-20) (Skinner 1982)

*The following questions concern information about your potential involvement with drugs, not including alcohol, over the last 12 months. Please answer **'yes'** or **'no'** to each of the following questions.*

1. Have you used drugs other than those used for medical reasons?
2. Have you abused prescription drugs?
3. Do you abuse more than one drug at a time?
4. Can you get through the week without using drugs?
5. Are you always able to stop using drugs when you want to?
6. Have you had 'blackouts' or 'flashbacks' as a result of drug use?
7. Do you feel bad or guilty about your drug use?
8. Does your spouse or parents ever complain about your involvement with drugs?
9. Has drug abuse created problems for you with your spouse or parents?
10. Have you lost friends because of your use of drugs?
11. Have you neglected your family because of your use of drugs?
12. Have you been in trouble at work because of your use of drugs?
13. Have you lost a job because of drug use?
14. Have you been involved in fights when under the influence of drugs?
15. Have you engaged in illegal activities in order to obtain drugs?
16. Have you been arrested for possession of illegal drugs?
17. Have you ever experience withdrawal symptoms when you stopped taking drugs?
18. Have you had medical problems as a result of your drug use?
19. Have you gone to anyone for help with a drug problem?
20. Have you been involved in a treatment programme specifically related to drugs?

Extra question: If you have ever smoked cannabis, would you say that over the last year you have been smoking it on at least a weekly basis?

Alcohol Use Disorders Identification Test (AUDIT) (Saunders 1993)

I am going to ask you some questions about your use of alcohol during the past year.

How often do you have a drink containing alcohol?

Never	0
Less than monthly	1
2 to 3 times a month	2
2 to 3 times a week	3
4 or more times a week	4

How many alcoholic drinks do you have on a typical drinking day?

None	0
1 or 2	1
3 or 4	2
5 or 6	3
7 or 9	4
10 or more	5

How often do you have six or more drinks on one occasion?

Never	0
Less than monthly	1
Monthly	2
Weekly	3
Daily or almost daily	4

How often during the last year have you found that you were unable to stop drinking once you had started?

Never	0
Less than monthly	1
Monthly	2
Weekly	3
Daily or almost daily	4

How often during the last year have you failed to do what was normally expected of you because of drinking?

Never	0
Less than monthly	1
Monthly	2
Weekly	3
Daily or almost daily	4

How often during the last year have you needed a drink first thing in the morning to get yourself going after a heavy drinking session?

Never	0
Less than monthly	1
Monthly	2
Weekly	3
Daily or almost daily	4

How often during the last year have you had a feeling of guilt or remorse after drinking?

Never	0
Less than monthly	1
Monthly	2
Weekly	3
Daily or almost daily	4

How often during the last year have you been unable to remember what happened the night before because you were drinking?

Never	0
Less than monthly	1
Monthly	2
Weekly	3
Daily or almost daily	4

Have you or someone else been injured as a result of your drinking?

Never	0
Less than monthly	1
Monthly	2
Weekly	3
Daily or almost daily	4

Has a relative, friend, doctor or other health worker been concerned about your drinking or suggested you cut down?

Never	0
Less than monthly	1
Monthly	2
Weekly	3
Daily or almost daily	4

HAMILTON RATING SCALE FOR DEPRESSION

(to be administered by a health care professional)

Patient's Name _____

Date of Assessment _____

To rate the severity of depression in patients who are already diagnosed as depressed, administer this questionnaire. The higher the score, the more severe the depression.

For each item, write the correct number on the line next to the item. (Only one response per item)

1. **DEPRESSED MOOD** (Sadness, hopeless, helpless, worthless)

_____
0= Absent
1= These feeling states indicated only on questioning
2= These feeling states spontaneously reported verbally
3= Communicates feeling states non-verbally—i.e., through facial expression, posture, voice, and tendency to weep
4= Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication

2. **FEELINGS OF GUILT**

_____
0= Absent
1= Self reproach, feels he has let people down
2= Ideas of guilt or rumination over past errors or sinful deeds
3= Present illness is a punishment. Delusions of guilt
4= Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. **SUICIDE**

_____
0= Absent
1= Feels life is not worth living
2= Wishes he were dead or any thoughts of possible death to self
3= Suicidal ideas or gesture
4= Attempts at suicide (any serious attempt rates 4)

4. **INSOMNIA EARLY**

_____
0= No difficulty falling asleep
1= Complains of occasional difficulty falling asleep—i.e., more than 1/2 hour
2= Complains of nightly difficulty falling asleep

5. **INSOMNIA MIDDLE**

_____
0= No difficulty
1= Patient complains of being restless and disturbed during the night
2= Waking during the night—any getting out of bed rates 2 (except for purposes of voiding)

Adapted from Hedlung and Vieweg. The Hamilton rating scale for depression. *Journal of Operational Psychiatry*. 1979;10(2):149-165.

6. **INSOMNIA LATE**

0= No difficulty
1= Waking in early hours of the morning but goes back to sleep
2= Unable to fall asleep again if he gets out of bed

7. **WORK AND ACTIVITIES**

0= No difficulty
1= Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
2= Loss of interest in activity; hobbies or work—either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
3= Decrease in actual time spent in activities or decrease in productivity
4= Stopped working because of present illness

8. **RETARDATION: PSYCHOMOTOR** (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

0= Normal speech and thought
1= Slight retardation at interview
2= Obvious retardation at interview
3= Interview difficult
4= Complete stupor

9. **AGITATION**

0= None
1= Fidgetiness
2= Playing with hands, hair, etc.
3= Moving about, can't sit still
4= Hand wringing, nail biting, hair-pulling, biting of lips

10. **ANXIETY (PSYCHOLOGICAL)**

0= No difficulty
1= Subjective tension and irritability
2= Worrying about minor matters
3= Apprehensive attitude apparent in face or speech
4= Fears expressed without questioning

11. **ANXIETY SOMATIC:** Physiological concomitants of anxiety, (i.e., effects of autonomic overactivity, "butterflies," indigestion, stomach cramps, belching, diarrhea, palpitations, hyperventilation, paresthesia, sweating, flushing, tremor, headache, urinary frequency). Avoid asking about possible medication side effects (i.e., dry mouth, constipation)

0= Absent
1= Mild
2= Moderate
3= Severe
4= Incapacitating

12. **SOMATIC SYMPTOMS (GASTROINTESTINAL)**

0= None
1= Loss of appetite but eating without encouragement from others. Food intake about normal
2= Difficulty eating without urging from others. Marked reduction of appetite and food intake

13. **SOMATIC SYMPTOMS GENERAL**

0= None
1= Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability
2= Any clear-cut symptom rates 2

14. **GENITAL SYMPTOMS** (Symptoms such as: loss of libido; impaired sexual performance; menstrual disturbances)

0= Absent
1= Mild
2= Severe

15. **HYPOCHONDRIASIS**

0= Not present
1= Self-absorption (bodily)
2= Preoccupation with health
3= Frequent complaints, requests for help, etc.
4= Hypochondriacal delusions

16. **LOSS OF WEIGHT**

A. When rating by history:
0= No weight loss
1= Probably weight loss associated with present illness
2= Definite (according to patient) weight loss
3= Not assessed

17. **INSIGHT**

0= Acknowledges being depressed and ill
1= Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2= Denies being ill at all

18. **DIURNAL VARIATION**

A. Note whether symptoms are worse in morning or evening. If NO diurnal variation, mark none
0= No variation
1= Worse in A.M.
2= Worse in P.M.

B. When present, mark the severity of the variation. Mark "None" if NO variation
0= None
1= Mild
2= Severe

19. **DEPERSONALIZATION AND DEREALIZATION** (Such as: Feelings of unreality; Nihilistic ideas)

0= Absent
1= Mild
2= Moderate
3= Severe
4= Incapacitating

20. **PARANOID SYMPTOMS**

0= None
1= Suspicious
2= Ideas of reference
3= Delusions of reference and persecution

21. **OBSESSIONAL AND COMPULSIVE SYMPTOMS**

0= Absent
1= Mild
2= Severe

Total Score _____

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Global Assessment of Functioning (GAF) Scale

Domain	1 - 10	11 - 20	21 - 30	31 - 40	41 - 50	51 - 60	61 - 70	71 - 80	81 - 90	91 - 100
Symptom Severity	Persistent danger of severely hurting self or others (e.g., recurrent violence) Or serious suicidal act with clear expectation of death. Or	Some danger of hurting self or others (e.g., suicide attempts without clear expectation of death; frequently violent; manic excitement) Or Gross impairment in communication (e.g., largely incoherent or mute) Or	Behavior is considerably influenced by delusions or hallucinations Or serious impairment in communication or judgment (e.g., sometimes incoherent, acts grossly inappropriately, suicidal preoccupation) Or	Some impairment in reality testing or communication (e.g., speech is at time illogical, obscure or irrelevant) Or	Serious symptoms (e.g., suicidal ideation, severe obsessional rituals, frequent shoplifting). Or	Moderate symptoms (e.g., flat affect and circumstantial speech, occasional panic attacks) Or	Some mild symptoms (e.g., depressed mood and mild insomnia) Or	If symptoms are present, they are transient and expectable reactions to psychosocial stressors (e.g., difficulty concentrating after family argument	Absent or minimal symptoms (e.g., mild anxiety before an exam), Generally satisfied with life. No more than everyday problems or concerns (e.g., an occasional argument with family members).	No symptoms
Level of Functioning	Persistent inability to maintain minimal personal hygiene	Occasionally fails to maintain minimal personal hygiene (e.g., smears feces)	Inability to function in almost all areas (e.g., stays in bed all day, no job, home or friends)	Major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood (e.g., depressed man avoids friend, neglects family, and is unable to work; child frequently beats up younger children, is defiant at home and is failing in school).	Any serious impairment in social, occupational, or school functioning (e.g., no friends, unable to keep a job).	Moderate difficulty in social, occupational, or school functioning (e.g., few friends, conflicts with co-workers).	Some difficulty in social, occupational or school functioning (e.g., occasional truancy, or theft within the household), but generally functioning pretty well, has some meaningful interpersonal relationships..	No more than slight impairment in social, occupational, or school functioning (e.g., temporarily falling behind in school work).	Good functioning in all areas, interested and involved in a wide range of activities, socially effective.	Superior functioning in a wide range of activities, life's problems never seem to get out of hand. Is sought out by others because of his or her many positive qualities

Clinical Global Impression of Illness Scale (Guy, 1976)

Severity of Illness (CGII)

Normal – not ill	1
Borderline illness	2
Mildly ill	3
Moderately ill	4
Markedly ill	5
Severely ill	6
Among most extremely ill	7

Clinical Global Impression (CGIC)

Very much improved	1
Much improved	2
Minimally improved	3
No change	4
Minimally worse	5
Much worse	6
Very much worse	7

Family Interview for Genetic Studies
NIMH 1999

FIGS: FACE SHEET

FAMILY INTERVIEW FOR GENETIC STUDIES (FIGS)

Interview date: [ ][ ] — [ ][ ] — [ ][ ][ ][ ]
Month Day Year

Family last name: _____ Family ID Number: [ ][ ][ ][ ]

Informant name: _____ _____ _____
First Middle Last

Informant ID: [ ][ ][ ][ ][ ]

Person being described name: _____ _____ _____
First Middle Last

Person being described ID: [ ][ ][ ][ ][ ]

Relationship to Informant: _____

Birthdate of person described, if known: [ ][ ] — [ ][ ] — [ ][ ][ ][ ]
Month Day Year

	No	Yes	Unk
Is person being described living?	0	1	9

Age and Year when last seen or known about, or died: Age [ ][ ] in Year [ ][ ][ ][ ]

If deceased, cause of death: _____

	No	Yes	Unk
Suicide?	0	1	9

INTERVIEWER: Refer to General Screening Questions if necessary.

1.	(**Probe:** has he/she had any psychiatric or personality problems like those we mentioned earlier?) Write narrative:	0	1	9

Continue Narrative:

FIGS: OTHER DISORDERS

1. Indicate any disorder not in the checklists and complete questions 1.a–f for the disorder.
   Specify: _____

   _____

Code Response

1.a) Code and describe professional treatment: 0 1 2 3 4 9

0. None

1. Inpatient: _____

2. Outpatient: _____

3. ECT: _____

4. Medication: _____

9. Unknown

Age

1.b) Age of onset [ ][ ]

Episodes

1.c) Number of episodes [ ][ ][ ]

Weeks

1.d) Duration of longest episode in weeks [ ][ ][ ]

Code Response

1.e) Rate and code impairment or incapacitation: 0 1 2 9

0. None
1. Impaired
2. Incapacitated
9. Unknown

1.f) Interviewer judgement on reliability of this information: 1 2 3

1. Good
2. Fair
3. Poor

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FIGS: GENERAL SCREENING QUESTIONS

Interview date: [ ][ ] — [ ][ ] — [ ][ ][ ][ ]
Month Day Year

Use One Per Informant

Family last name: _____ Family ID Number: [ ][ ][ ][ ]

Informant name: _____ ____ _____ ID: [ ][ ][ ][ ][ ]
First MI Last

INTERVIEWER: Before you begin, you need to generate or obtain a pedigree on which to record all of the responses to the following General Screening Questions. (See FIGS Manual for details.)

Step 1: *Let's go over your family tree.* (Include spouse and his/her parents and siblings, offspring, parents, siblings, aunts, uncles, cousins, grandparents, as well as any other relatives the informant can recall.)

Step 2: *Now I am asking you to keep in mind all those in your family tree as I go through this list of questions.* (Note all positive responses on the pedigree.)

Was anyone adopted?

Was anyone mentally retarded?

Did anyone:

Have problems with their nerves or emotions? Take medicine or see a doctor for it? Take lithium?

Feel very low for a couple of weeks or more, or have a diagnosis of depression?

Attempt or complete suicide?

Seem overexcited (or manic) day and night, or have a diagnosis of mania?

Have visions, hear voices, or have beliefs that seem strange or unreal?

Have unusual or bizarre behavior, or have a diagnosis of schizophrenia?

Have trouble with the police, with completing school, or with keeping a job?

Have alcohol or drug use that caused problems (with health, family, job, or police)? Go to AA or NA, or have treatment for this?

(Was anyone) hospitalized for psychiatric problems, or for drug or alcohol problems?

Have inherited medical diseases such as Huntington's disease or seizure disorder or any other disorders of the brain or nervous system?

(Did anyone) have few friends, or seem to be a loner?

(Did anyone) seem odd or eccentric in behavior or appearance?

(Was anyone) extremely jealous, or suspicious, or believe in magic, or see special meanings in things that no one else saw?

Step 3: Complete a Face Sheet for each of the informant's first degree relatives and spouse. If he/she knows well other affected relatives, also complete a Face Sheet for them. In addition, for each of these given a positive response in the General Screening, complete the symptom checklist for any suspected: Depression/Mania, Alcohol/Drug Abuse, Psychosis, or Paranoid/Schizoid/Schizotypal Personality.

FIGS: DEPRESSION CHECKLIST

Interview date: ☐☐ — ☐☐ — ☐☐☐☐
Month Day Year

Family last name: _____ Family ID Number: ☐☐☐☐

Informant name: _____ ___ _____ ID: ☐☐☐☐☐
First MI Last

Person being described name: _____ ___ _____ ID: ☐☐☐☐☐
First MI Last

Code for a single episode (best recalled, worst episode if possible).

		No	Yes	Unk
1.	*During depression...*			
1.a)	*...was he/she depressed most of the day, nearly every day, for as long as a week or more?*	0	1	9
1.b)	*...did he/she lose interest in things or become unable to enjoy most things, for as long as a week?*	0	1	9
1.c)	*...did he/she have a change in appetite or weight without trying to?*	0	1	9
1.d)	*...did he/she have a change in sleep patterns (either too much or too little)?*	0	1	9
1.e)	*...did he/she become unable to work, go to school, or take care of household responsibilities?*	0	1	9

If yes: Describe: _____

_____

Discontinue this checklist ◄

1.f)	*...did he/she move or speak more slowly than usual?*	0	1	9
1.g)	*...did he/she pace or wring his/her hands?*	0	1	9
1.h)	*...did he/she have less energy or feel tired out?*	0	1	9
1.i)	*...did he/she feel guilty, worthless or blame himself/herself?*	0	1	9
1.j)	*...did he/she have trouble concentrating or making decisions?*	0	1	9
1.k)	*...did he/she talk of death or suicide? Or try suicide?*	0	1	9
1.l)	*...did he/she have visions, or hear voices, or have beliefs or behavior that seem strange or unusual, at the same time as (symptoms above)?* (If **YES**, complete a Psychosis Checklist after this one.)	0	1	9

FIGS: DEPRESSION CHECKLIST

Code Response

2. Code and describe professional treatment: 0 1 2 3 4 9

   0. None
   1. Inpatient: _____
   2. Outpatient: _____
   3. ECT: _____
   4. Medication: _____
   9. Unknown

3. Age of onset — Age [ ][ ]

4. Number of episodes — Episodes [ ][ ][ ]

5. Duration of longest episode in weeks — Weeks [ ][ ][ ]

Code Response

6. Rate and code impairment or incapacitation: 0 1 2 3 4 9

   0. None
   1. Modified RDC Impairment
   2. Modified RDC Incapacitation
   3. RDC Minor Role Dysfunction
   4. Change from previous functioning
   9. Unknown

7. Interviewer judgement on reliability of this information: 1 2 3

   1. Good
   2. Fair
   3. Poor

FIGS: MANIA CHECKLIST

Interview date: ☐☐☐ — ☐☐ — ☐☐☐☐
Month Day Year

Family last name: _____ Family ID Number: ☐☐☐☐

Informant name: _____ ___ _____ ID: ☐☐☐☐☐
First MI Last

Person being described name: _____ ___ _____ ID: ☐☐☐☐☐
First MI Last

		No	Yes	Unk
1.	*For most of the time day and night over several days, did he/she (more than usual)...*			
1.a)	*...seem too happy/high/excited?*	0	1	9
1.b)	*...become so excited or agitated it was impossible to converse with him/her?*	0	1	9
1.c)	*...act very irritable or angry?*	0	1	9
1.d)	*...need less sleep without feeling tired?*	0	1	9
1.e)	*...show poor judgement (e.g., spending sprees, sexual indiscretions?)*	0	1	9

If yes: Describe: _____

_____

Discontinue this checklist

1.f)	*...behave in such a way as to cause difficulty for those around him/her* (obnoxious/manipulative)*?*	0	1	9
1.g)	*...feel that he/she had special gifts or powers?*	0	1	9
1.h)	*...become more talkative than usual?*	0	1	9
1.i)	*...jump from one idea to another?*	0	1	9
1.j)	*...become easily distracted?*	0	1	9
1.k)	*...get involved in too many activities at work or school?*	0	1	9
1.l)	*...have visions? hear voices? have beliefs or behavior that seem strange or unusual? at the same time as (above symptoms)?* (If **YES**, complete a Psychosis Checklist after this one.)	0	1	9

FIGS: MANIA CHECKLIST

Code Response

2. Code and describe professional treatment: 0 1 2 3 4 9

   0. None
   1. Inpatient: _____
   2. Outpatient: _____
   3. ECT: _____
   4. Medication: _____
   9. Unknown

Age

3. Age of onset [ ][ ]

Episodes

4. Number of episodes [ ][ ][ ]

Weeks

5. Duration of longest episode in weeks [ ][ ][ ]

Code Response

6. Rate and code impairment or incapacitation: 0 1 2 9

   0. None
   1. Impaired
   2. Incapacitated
   9. Unknown

7. Interviewer judgement on reliability of this information: 1 2 3

   1. Good
   2. Fair
   3. Poor

FIGS: ALCOHOL & DRUG ABUSE CHECKLIST

Interview date: [ ][ ] — [ ][ ] — [ ][ ][ ][ ]
Month Day Year

Family last name: _____ Family ID Number: [ ][ ][ ][ ]

Informant name: _____ ___ _____ ID: [ ][ ][ ][ ][ ]
First MI Last

Person being described name: _____ ___ _____ ID: [ ][ ][ ][ ][ ]
First MI Last

ALCOHOLISM

Code for a single episode (best recalled, worst episode if possible).

		No	Yes	Unk
1.	*Because of drinking, did he/she ever have problems such as...*			
1.a)	*...being unable to stop or cut down on drinking?*	0	1	9
1.b)	*...spending a lot of time drinking or being hung over?*	0	1	9
1.c)	*...being unable to work, go to school, or take care of household responsibilities?*	0	1	9
1.d)	*...being high from drinking when he/she could get hurt?*	0	1	9
1.e)	*...accidental injuries?*	0	1	9
1.f)	*...reducing or giving up important activities?*	0	1	9
1.g)	*...objections from the family or friends, at work or school?*	0	1	9
1.h)	*...legal problems more than once (DWIs, arrests)?*	0	1	9
1.i)	*...blackouts more than once?*	0	1	9
1.j)	*...binges or benders more than once?*	0	1	9
1.k)	*...physical health problems (liver disease, pancreatitis)?*	0	1	9
1.l)	*...emotional or psychological problems (uninterested, depressed, suspicious/paranoid, having strange ideas)?*	0	1	9
1.m)	*...withdrawal symptoms (shakes, seizures/convulsions, DTs)?*	0	1	9

Code Response

2. *Did he/she go to AA or have any kind of treatment?* (Code and describe all that apply) — 0 1 2 3 4 9

0. None
1. Inpatient: _____
2. Outpatient: _____
3. AA or other self-help: _____
4. Medication: _____
9. Unknown

Describe details and/or other treatment:

		No	Yes	Unk
3.	*Does he/she currently have a problem with alcohol?*	0	1	9

FIGS: ALCOHOL & DRUG ABUSE CHECKLIST

4. Record age he/she began to have alcohol-related problems. Ons Age [ ][ ]

5. Record age he/she stopped drinking heavily. Rec Age [ ][ ]

DRUG ABUSE/DEPENDENCE

6. *Which drugs did he/she have trouble with?*

Specify: _____

		No	Yes	Unk
7.	*Because of his/her drug use, did he/she have...*			
7.a)	*... physical health problems (hepatitis, overdose, withdrawal symptoms, accidental injuries)?*	0	1	9
7.b)	*... emotional or psychological problems (uninterested, depressed, suspicious/paranoid, having strange ideas)?*	0	1	9
7.c)	*... legal problems (arrests for possessing, selling, or stealing drugs)?*	0	1	9
7.d)	*... problems with family or friends?*	0	1	9
7.e)	*... troubles at work or school?*	0	1	9

Code Response

8. *Did he/she go to NA or have any kind of treatment?* (Code and describe all that apply) 0 1 2 3 4 9

0. None
1. Inpatient: _____
2. Outpatient: _____
3. NA or other self-help: _____
4. Medication: _____
9. Unknown

Describe details and/or other treatment:

		No	Yes	Unk
9.	*Does he/she currently have a problem with drugs?*	0	1	9

10. Record age he/she began to have drug-related problems. Ons Age [ ][ ]

11. Record age he/she stopped using drugs heavily. Rec Age [ ][ ]

Code Response

12. Interviewer judgement on reliability of this information: 1 2 3

1. Good
2. Fair
3. Poor

FIGS: PSYCHOSIS CHECKLIST

Interview date: [ ][ ] — [ ][ ] — [ ][ ][ ][ ]
Month Day Year

Family last name: _____ Family ID Number: [ ][ ][ ][ ]

Informant name: _____ ___ _____ ID: [ ][ ][ ][ ][ ]
First MI Last

Person being described name: _____ ___ _____ ID: [ ][ ][ ][ ][ ]
First MI Last

PSYCHOSIS

Code for a single episode (best recalled, worst episode if possible).

1. *What were his/her unusual beliefs or experiences?*

Specify: _____

_____

	Did he/she ever...	No	Yes	Unk
1.a)	*...believe people were following him/her, or that someone was trying to hurt or poison him/her?*	0	1	9
1.b)	*...believe someone was reading his/her mind?*	0	1	9
1.c)	*...believe he/she was under the control of some outside person or power or force?*	0	1	9
1.d)	*...believe his/her thoughts were broadcast, or that an outside force took away his/her thoughts or put thoughts into his/her head?*	0	1	9
1.e)	*...have any other strange or unusual beliefs?*	0	1	9

If yes: Describe: _____

_____

1.f)	*...see things that were not really there?*	0	1	9
1.g)	*...hear voices or other sounds that were not real?*	[0]	1	9

If yes: Describe: _____

_____

Skip to question 1.h

FIGS: PSYCHOSIS CHECKLIST

		No	Yes	Unk
1.g.1)	(Code **YES** if: voice with content having no relation to depression or elation, or voice keeping up running commentary on subject's behavior or thoughts, or two or more voices conversing.)	0	1	9
1.h)	*...speak in a way that was difficult to make sense of?*	0	1	9

If yes: Describe: _____

_____

1.i)	*...seem to be physically stuck in one position, or move around excitedly without any purpose?*	0	1	9
1.j)	*...appear to have no emotions, or inappropriate emotions?*	0	1	9

2. *How long did the longest of these experiences last?* Weeks [ ][ ][ ]

INTERVIEWER: If less than 1 week (unless successfully treated), STOP HERE. Otherwise continue, if informant is knowledgeable about this person.

INTERVIEWER: If subject did NOT have any episode of Major Depression or Mania (by FIGS checklists from this informant), skip to question 6.

		No	Yes	Unk
3.	*When any* (SX above) *happened, did he/she also have the mood disturbance we discussed before, at the same time?*	0	1	9

Skip to question 6

INTERVIEWER: For the rest of this checklist, "illness duration" refers to total time of illness, including active and prodromal and/or residual symptoms and/or treatment (include time on medication).

		No	Yes	Unk
4.	(Probe and code **YES** if mania and/or depression lasted at least 30% of total duration of illness described above, or medication for it.)	0	1	9
5.	(Probe and code **YES** if illness described above, or medication for it, was ever present for as long as one week, without depression and/or mania.)	0	1	9

Skip to question 6

5.a)	(Code **YES** if the above was true for as long as two weeks.)	0	1	9

Code Response

6. Code and describe professional treatment (Code and describe all that apply): 0 1 2 3 4 9

   0. None
   1. Inpatient: _____
   2. Outpatient: _____
   3. ECT: _____
   4. Medication: _____
   9. Unknown

   Describe details and/or other treatment:

7. Age of onset — Age [ ][ ]

8. Number of episodes (Code **001** if chronic symptoms and/or treatment since onset) — Episodes [ ][ ][ ]

9. Total illness duration (all episodes, includes active and prodromal and/or residual symptoms and/or treatment. — Weeks [ ][ ] OR Years [ ][ ]

   Code Response

10. Rate and code impairment or incapacitation: 0 1 2 9

    0. None
    1. Impaired
    2. Incapacitated
    9. Unknown

11. Interviewer judgement on reliability of this information: 1 2 3

    1. Good
    2. Fair
    3. Poor

INTERVIEWER: If informant apparently does not know subject well enough to give information on Prodromal/Residual symptoms, STOP HERE.

If duration criterion for DSM III-R Schizophrenia, Chronic Type, already met, (question 9, total illness duration > 2 years), STOP HERE.

FIGS: PSYCHOSIS CHECKLIST

INTERVIEWER: Use this page only if Schizo-affective is ruled out (by questions 3 to 5 above), or if the psychosis symptoms lasted at least one week (or shorter duration if successfully treated).

Establishing the Prodromal Period:

16. *Now I would like to ask you about the year before his/her* **(psychotic symptoms)** *started. During that time did he/she...*

(Ask after completing question 16.a-n for the Prodromal period:)
Establishing the Residual Period:

Now I would like to ask you about the year after his/her **(psychotic symptoms)** *stopped. During that time did he/she...*

	Prodromal Period			**Residual Period**		
	No	Yes	Unk	No	Yes	Unk
16.a) ...*stay away from family and friends, become socially isolated?*	0	1	9	0	1	9
16.b) ...*have trouble doing his/her job, going to school, or doing work at home?*	0	1	9	0	1	9
16.c) ...*do something peculiar like talking to self in public?*	0	1	9	0	1	9
16.d) ...*neglect hygiene and grooming?*	0	1	9	0	1	9
16.e) ...*appear to have no emotions or inappropriate emotions?*	0	1	9	0	1	9
16.f) ...*speak in a way that was hard to understand, or was he/she at a loss for words?*	0	1	9	0	1	9
16.g) ...*have unusual beliefs or ideas?*	0	1	9	0	1	9
16.h) ...*have unusual perceptions, like sensing the presence of a person not actually present?*	0	1	9	0	1	9
16.i) ...*have no interests, no energy?*	0	1	9	0	1	9
16.j) ...*find special meaning in TV, radio, or newspaper articles?*	0	1	9	0	1	9
16.k) ...*feel nervous with other people?*	0	1	9	0	1	9
16.l) ...*worry that people were out to get him/her?*	0	1	9	0	1	9

	Weeks
17.a) *How long did he/she have these experiences?*	

INTERVIEWER: Return to top of question 16 to establish the Residual period and code in Residual Column.

	Weeks			
17.b) *How long did he/she have these experiences after his/her* **(Active psychotic features)** *stopped?*				
			No	Yes	Unk
18. *Was he/she always this way?*			0	1	9

FIGS: PARANOID/SCHIZOID/SCHIZOTYPAL PERSONALITY CHECKLIST

SITE OPTIONAL

Interview date: [ ][ ][ ] — [ ][ ] — [ ][ ][ ][ ]
Month Day Year

Family last name: _____ Family ID Number: [ ][ ][ ][ ]

Informant name: _____ ___ _____ ID: [ ][ ][ ][ ][ ]
First MI Last

Person being described name: _____ ___ _____ ID: [ ][ ][ ][ ][ ]
First MI Last

PARANOID PERSONALITY

Code for a single episode (best recalled, worst episode if possible).

		No	Yes	Unk
1.	*Does he/she...*			
1.a)	*...often keep an eye out to stop people from taking advantage of him/her?* Expects, without sufficient basis, to be exploited/harmed by others.	0	1	9
1.b)	*...get concerned that friends or co-workers are not really loyal or trustworthy?* Questions, without justification, loyalty of friends or associates.	0	1	9
1.c)	*...often pick up hidden threats or put-downs from what people say or do?* Reads hidden demeaning or threatening meanings into benign remarks or events.	0	1	9
1.d)	*...take a long time to forgive someone if they have insulted or hurt him/her?* Bears grudges or unforgiving of insults/slights.	0	1	9
1.e)	*...seem to believe it is best not to let other people know much about him/her?* Reluctant to confide in others because of unwarranted fear that information will be used against him/her.	0	1	9
1.f)	*...often get angry about being insulted or slighted?* Easily slighted, quick to react with anger or counterattack.	0	1	9
1.g)	*...seem to be a jealous person? Ever suspected that his/her spouse/partner was unfaithful?* Questions, without justification, fidelity of spouse or sexual partner.	0	1	9

SCHIZOID PERSONALITY

		No	Yes	Unk
2.	*Does he/she...*			
2.a)	*...seem not to want or enjoy close relationships, like with family or friends?* Neither desires nor enjoys close relationships, including family.	0	1	9
2.b)	*...prefer to do things alone rather than with other people?* Almost always chooses solitary activities.	0	1	9
2.c)	*...hardly ever seem to have strong feelings, like being very angry or very happy?* Rarely, if ever, claims or appears to experience strong emotions, anger/joy.	0	1	9
2.d)	*...seem uninterested in being sexually involved with another person?* Little if any desire to have sexual experiences with another person (age taken into account).	0	1	9

SITE OPTIONAL

		No	Yes	Unk
2.e)	*...seem not to care if people praise or criticize him/her?* Indifferent to praise and criticism from others.	0	1	9
2.f)	*...have no one to be really close to or confide in, or just one person, outside of the immediate family?* No close friends or confidants, or only one, other than first-degree relatives.	0	1	9
2.g)	*...act cold or distant, hardly ever smile or nod back at people?* Constricted affect, aloof, cold, rarely reciprocates gestures or expressions.	0	1	9

SCHIZOTYPAL PERSONALITY

3. *Does he/she...*

3.a)	*...wonder if people talking to each other are talking about him/her? Say that a common event or object is a special sign for him/her?* Ideas of reference (not delusions of reference).	0	1	9
3.b)	*...often act nervous in a group of unfamiliar people?* Excessive social anxiety.	0	1	9
3.c)	*...reports experiences with the supernatural? Believe in astrology, seeing the future, UFOs, ESP or a "sixth sense"?* Odd beliefs or magical thinking, influencing behavior and inconsistent with subcultural norms.	0	1	9
3.d)	*...mistake objects or shadows for people, or noises for voices? Have a sense that some invisible person or force is around? See faces change before his/her eyes?* Unusual perceptual experiences.	0	1	9
3.e)	*...behave in odd or eccentric ways? Look peculiar or untidy, have unusual mannerisms, talk to him/herself?* Odd, eccentric, peculiar behavior or appearance.	0	1	9
3.f)	*...sometimes make it hard to follow what he/she is saying? Ramble off the subject, talk in vague or abstract terms?* Odd speech (without loosened associations or incoherence).	0	1	9
3.g)	*...sometimes act silly, not in keeping with the situation? Or tend not to show any feelings in response to people?* Inappropriate or constricted affect (e.g., silly or aloof).	0	1	9

INTERVIEWER: If any **YES** to any Personality Disorders, ask the following questions (to be used for research, not diagnosis).

IMPAIRMENT/DISTRESS

4.	*Does he/she have problems because of this behavior or thinking or feeling—either with the family or socially, or at work or school?* Significant social or occupational impairment.	0	1	9
5.	*Does this behavior or thinking or feeling cause the person unhappiness?* Significant subjective distress.	0	1	9

		Code Response		
		1	2	3
6.	Interviewer judgement on reliability of this information: 1. Good 2. Fair 3. Poor			

Annett Handedness Inventory

Name

Study number

Please indicate which hand you prefer to use for the following activities by putting a tick in the appropriate column.

RR **You would always use your right hand**

R **You prefer using your right hand**

E **You have no particular preference for either hand**

L **You prefer using your left hand**

LL **You would always use your left hand**

Please try to act each task through before answering and do not assume that the same hand will be preferred throughout.

		LL	L	E	R	RR
1.	Throwing a dart					
2.	Using an electric iron					
3.	Painting a picture					
4.	Using a toothbrush					
5.	Using a table-tennis bat					
6.	Pushing in a drawing pin					
7.	Polishing shoes					
8.	Throwing a ball					
9.	Rubbing something out					
10.	Combing your hair					
11.	Slicing bread					
12.	Using a corkscrew					
13.	Striking a match					
14.	Hammering					
15.	Sawing wood					
16.	Pouring water					
17.	Handwriting					

Q As far as you are aware, are you colour-blind? Y N

Q How many years have you been in full-time education? .....

N A R T (answer/record sheet)

Initials ..... Research No ..... Date .....

Pronunciation guide

CHORD	kôrd	SUPERFLUOUS	sōō-pûr'flŏŏ-əs, sū-pûr'flŏŏ-əs
CHE	āk	SIMILE	sim'i-li
DEPOT	dep'ō	BANAL	bən-al'
ISLE	īl	QUADRUPED	kwod'rŏŏ-ped
BOUQUET	bōōk'ā, bōōkā', bōkā'	CELLIST	chel'ist
PSALM	säm	FACADE	fa-säd'
WEAPON	kā'pn	ZEALOT	zel'ət
DENY	di-nī	DRACHM	dram
NAUSEA	nō'si-ə, nō'zhə	AEON	ē'on
DEBT	det	PLACEBO	plə-sē'bō
COURTEOUS	kûrt'yəs	ABSTEMIOUS	ab-stē'mi-əs
RAREFY	râr'-i-fī	DETENTE	dā-tāt (Fr.)
EQUIVOCAL	i-kwiv'ə-kl	IDYLL	id'il, id'əl
NAIVE	nä-ēv	PUERPERAL	pū-ûr'pər-əl
CATACOMB	kat'ə-kōōm	AVER	ə-vûr'
BOLED	jāld	GAUCHE	gō sh
CYME	tīm	TOPIARY	tō'pi-ə-ri
AIR	âr	LEVIATHAN	le-vī'ə-thən
INDEX	rā'diks	BEATIFY	bi-at'i-fī
ASSIGNATE	as'-ig-nāt	PRELATE	prel'it
CETUS	hī-ā'təs	SIDEREAL	sī-dē'ri-əl
SUBTLE	sut'l	DEMESNE	di-mān', di-mēn'
PROCREATE	prō'kri-āt	SYNCOPE	sing'kə-pē
JET	jist	LABILE	lā'bīl
HUGE	gowj	CAMPANILE	kam-pan-ē'lā, kam-pan-ē'lē

ERROR SCORE =

PREDICTED VERBAL IQ =

PREDICTED FULL SCALE IQ =

CHORD

ACHE

DEPOT

AISLE

BOUQUET

PSALM

CAPON

DENY

NAUSEA

DEBT

COURTEOUS

RAREFY

EQUIVOCAL

NAIVE

CATACOMB

GAOLED

THYME

HEIR

RADIX

ASSIGNATE

HIATUS

SUBTLE

PROCREATE

GIST

GOUGE

SUPERFLUOUS

SIMILE

BANAL

QUADRUPED

CELLIST

FACADE

ZEALOT

DRACHM

AEON

PLACEBO

ABSTEMIOUS

DETENTE

IDYLL

PUERPERAL

AVER

GAUCHE

TOPIARY

LEVIATHAN

BEATIFY

PRELATE

SIDEREAL

DEMESNE

SYNCOPE

LABILE

CAMPANILE

1:

The WAIS-R Full Scale, Verbal and Performance IQs predicted from the number of errors made on RT.

T rs	Predicted Full Scale IQ	Predicted Verbal IQ	Predicted Performance IQ	NART Errors	Predicted Full Scale IQ	Predicted Verbal IQ	Predicted Performance IQ
	131	127	128	25	100	99	100
	129	126	127	26	98	98	99
	128	125	126	27	97	97	98
	127	124	125	28	96	95	97
	126	123	123	29	95	94	96
	124	122	122	30	94	93	95
	123	121	121	31	92	92	94
	122	119	120	32	91	91	93
	121	118	119	33	90	90	91
	120	117	118	34	89	89	90
	118	116	117	35	87	87	89
	117	115	116	36	86	86	88
	116	114	115	37	85	85	87
	115	113	114	38	84	84	86
	113	111	112	39	82	83	85
	112	110	111	40	81	82	84
	111	109	110	41	80	81	83
	110	108	109	42	79	80	82
	108	107	108	43	77	78	80
	107	106	107	44	76	77	79
	106	105	106	45	75	76	78
	105	103	105	46	74	75	77
	103	102	104	47	73	74	76
	102	101	102	48	71	73	75
	101	100	101	49	70	72	74
				50	69	70	73

ng these tables,

SE est of Full Scale IQ = 8.6
SE est of Verbal IQ = 7.3
SE est of Performance IQ = 11.5

6 BLOCK DESIGN Discontinue after 3 consecutive failures.

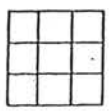
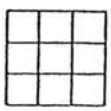
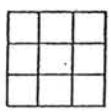
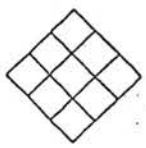
Design	Time	Pass-Fail	Score (Circle the appropriate score for each design.)
60″	1		2
	2		0 1
60″	1		2
	2		0 1
60″			0 — 16-60: 4 — 11-15: 5 — 1-10: 6
60″			0 — 16-60: 4 — 11-15: 5 — 1-10: 6
60″			0 — 21-60: 4 — 16-20: 5 — 11-15: 6 — 1-10: 7
120″			0 — 36-120: 4 — 26-35: 5 — 21-25: 6 — 1-20: 7
120″			0 — 61-120: 4 — 46-60: 5 — 31-45: 6 — 1-30: 7
120″			0 — 76-120: 4 — 56-75: 5 — 41-55: 6 — 1-40: 7
120″			0 — 76-120: 4 — 56-75: 5 — 41-55: 6 — 1-40: 7

Total Max = 51

rect solutions

1  2  3  4  5  6  7  8  9 

ch incorrect solutions offered by the examinee.

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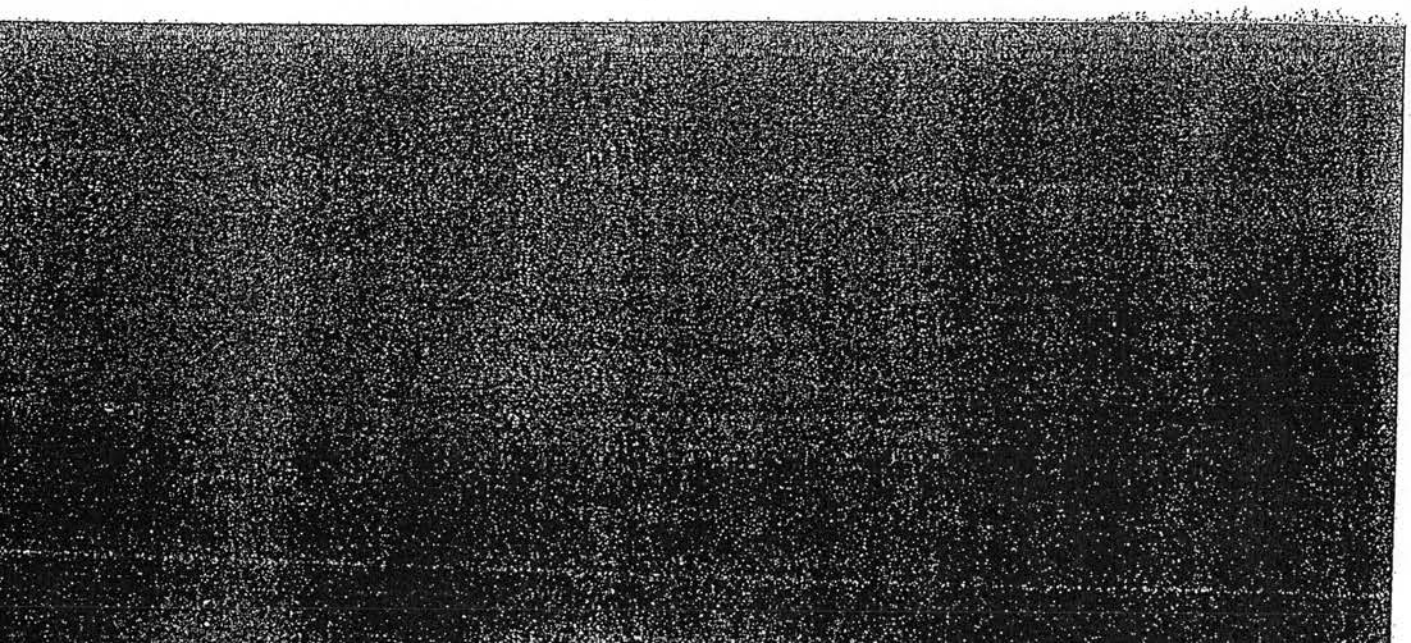


DATE..... ID..... RNO..... RIGHT / LEFT HANDED

TRIAL 1		
DRILL		S
PLUMS		E
VEST		;
PARSLEY		P
GRAPES		W
PAPRIKA		O
SWEATER		L
WRENCH		F
CHIVES		U
TANGERINES		R
CHISEL		A
JACKET		J
NUTMEG		I
APRICOTS		Q
PLIERS		D
SLACKS		K
TOTAL		

TRIAL 2		
DRILL		S
PLUMS		E
VEST		;
PARSLEY		P
GRAPES		W
PAPRIKA		O
SWEATER		L
WRENCH		F
CHIVES		U
TANGERINES		R
CHISEL		A
JACKET		J
NUTMEG		I
APRICOTS		Q
PLIERS		D
SLACKS		K
TOTAL		

TRIAL 3		
DRILL		S
PLUMS		E
VEST		;
PARSLEY		P
GRAPES		W
PAPRIKA		O
SWEATER		L
WRENCH		F
CHIVES		U
TANGERINES		R
CHISEL		A
JACKET		J
NUTMEG		I
APRICOTS		Q
PLIERS		D
SLACKS		K
TOTAL		

TRIAL 4		
DRILL		S
PLUMS		E
VEST		;
PARSLEY		P
GRAPES		W
PAPRIKA		O
SWEATER		L
WRENCH		F
CHIVES		U
TANGERINES		R
CHISEL		A
JACKET		J
NUTMEG		I
APRICOTS		Q
PLIERS		D
SLACKS		K
TOTAL		

TRIAL 5		
DRILL		S
PLUMS		E
VEST		;
PARSLEY		P
GRAPES		W
PAPRIKA		O
SWEATER		L
WRENCH		F
CHIVES		U
TANGERINES		R
CHISEL		A
JACKET		J
NUTMEG		I
APRICOTS		Q
PLIERS		D
SLACKS		K
TOTAL		

RNO.....

LIST B		
TOASTER		;
CHERRIES		Q
HALIBUT		D
GINGER		I
PINEAPPLE		R
SPATULA		L
OREGANO		O
FLOUNDER		S
SAGE		P
LEMONS		W
COD		A
SKILLET		K
PEACHES		E
SALMON		F
CINNAMON		U
BOWL		J
TOTAL		

SHORT DELAY		
DRILL		S
PLUMS		E
VEST		;
PARSLEY		P
GRAPES		W
PAPRIKA		O
SWEATER		L
WRENCH		F
CHIVES		U
TANGERINES		R
CHISEL		A
JACKET		J
NUTMEG		I
APRICOTS		Q
PLIERS		D
SLACKS		K
TOTAL		

SHORT DELAY CUED RECALL

SPICES AND HERBS - 1

PARSLEY		P
PAPRIKA		O
CHIVES		U
NUTMEG		I

FRUIT - 3

PLUMS		E
GRAPES		W
TANGERINES		R
APRICOTS		Q

TOOLS - 2

DRILL		S
WRENCH		F
CHISEL		A
PLIERS		D

CLOTHING - 4

VEST		;
SWEATER		L
JACKET		J
SLACKS		K

DELAY		
DRILL		S
PLUMS		E
VEST		;
PARSLEY		P
GRAPES		W
PAPRIKA		O
SWEATER		L
WRENCH		F
CHIVES		U
TANGERINES		R
CHISEL		A
JACKET		J
NUTMEG		I
APRICOTS		Q
PLIERS		D
SLACKS		K
TOTAL		

SPICES AND HERBS - 1

PARSLEY		P
PAPRIKA		O
CHIVES		U
NUTMEG		I

FRUIT - 3

PLUMS		E
GRAPES		W
TANGERINES		R
APRICOTS		Q

TOOLS - 2

DRILL		S
WRENCH		F
CHISEL		A
PLIERS		D

CLOTHING - 4

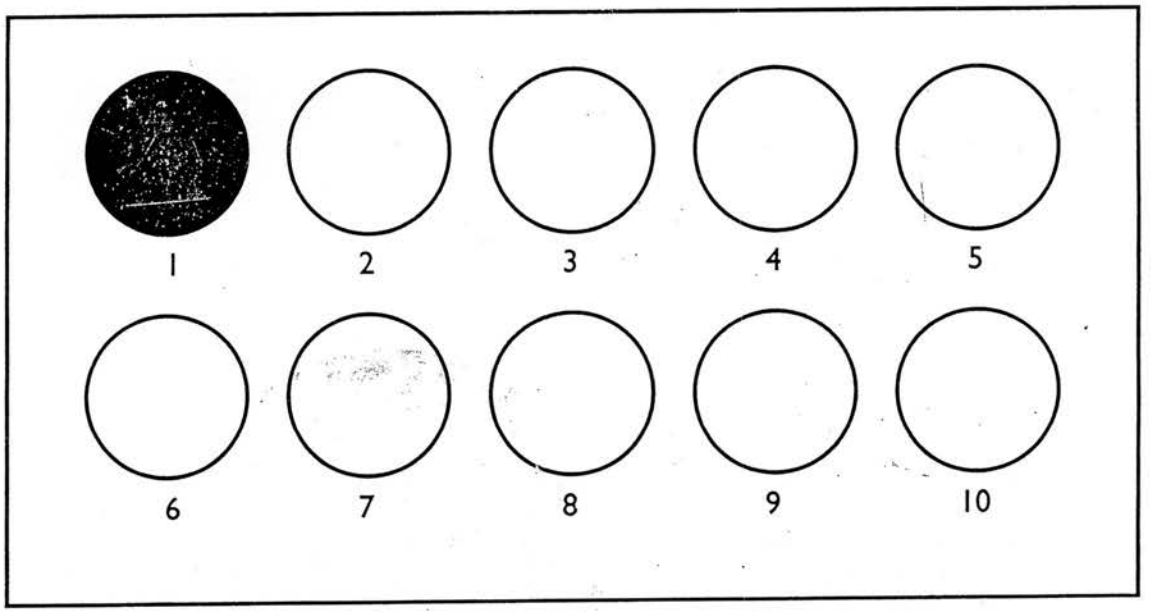
VEST		;
SWEATER		L
JACKET		J
SLACKS		K

R.NO.....

LONG DELAY RECOGNITION

SWEATER	
OREGANO	
FLOUNDER	
RUGS	
TIRES	
PEPPER	
JACKET	
ASPRIN	
WAX	
DRILL	
APRICOTS	
SPATULA	
CHERRIES	
DRUMS	
CHIVES	
FILM	
CHISEL	
BRIEFCASE	
PASTRY	
TANGERINES	
CLOCK	
SHOES	
GRAPES	
SALMON	
PAPRIKA	
RACKET	
GINGER	
SLACKS	
BOOKS	
PARSLEY	
VEST	
APPLES	
GRILL	
PLUMS	
WRENCH	
LEMONS	
TAPES	
VITAMINS	
PLIERS	
BOWL	
HAMMER	
NUTMEG	
CHIMES	
SOAP	

TVTC
Thames Valley
Test Company



the **Brixton** test

[isbn **1 874261 26 1**]

The Brixton Spatial Anticipation Test

- *'There are many pages here which all have the same basic design on them. There are always ten positions, and one of them is always coloured blue'* [point to filled circle on page one]. *'However the coloured one moves around according to various patterns that come and go without warning. These numbers* [point to numbers underneath the circles] *are just here to refer to the position – there is nothing complicated or mathematical about this test'.*
- *'Now, as I turn the pages over, your job is to pick up on the pattern as best you can, and point to where you think the blue one is going to be on the next page. It's not guess-work – you can work it out. For instance, imagine the blue one was here* [point to position 6], *and then when I turn the page it goes to 7, and then to 8, then to 9 – you might reasonably expect it next to go to 10'.*
- *'From time to time the pattern changes without warning, and then it is your job to pick up on the new pattern as best you can. Do you understand?'*
- Give further assistance if necessary
- *'Obviously the first time you have nothing to go on, so your first answer will have to be a guess – have a guess as to where the blue one will be next'*

Item/ page	Correct answer	Subject's response	Correct/ incorrect
1	any		
2	3		☐
3	4		☐
4	5		☐
5	6		☐
6 *	7		☐
7	4		☐
8	3		☐
9	2		☐
10	1		☐
11	10		☐
12 *	9		☐
13	10		☐
14	5		☐
15	10		☐
16	5		☐
17	10		☐
18	5		☐
19 *	10		☐
20	7		☐
21	8		☐
22	9		☐
23	10		☐
24	1		☐
25	2		☐
26 *	3		☐
27	10		☐
28	9		☐
29 *	8		☐
30	1		☐
31	2		☐
32	3		☐
33	4		☐
34 *	5		☐
35	4		☐
36	10		☐
37	4		☐
38	10		☐
39	4		☐
40	10		☐
41 *	4		☐
42	9		☐
43	9		☐
44	9		☐
45	9		☐
46	9		☐
47	9		☐
48 *	9		☐
49	9		☐
50	8		☐
51	9		☐
52	8		☐
53	9		☐
54	8		☐
55	9		☐

Total number of errors (raw score) ←

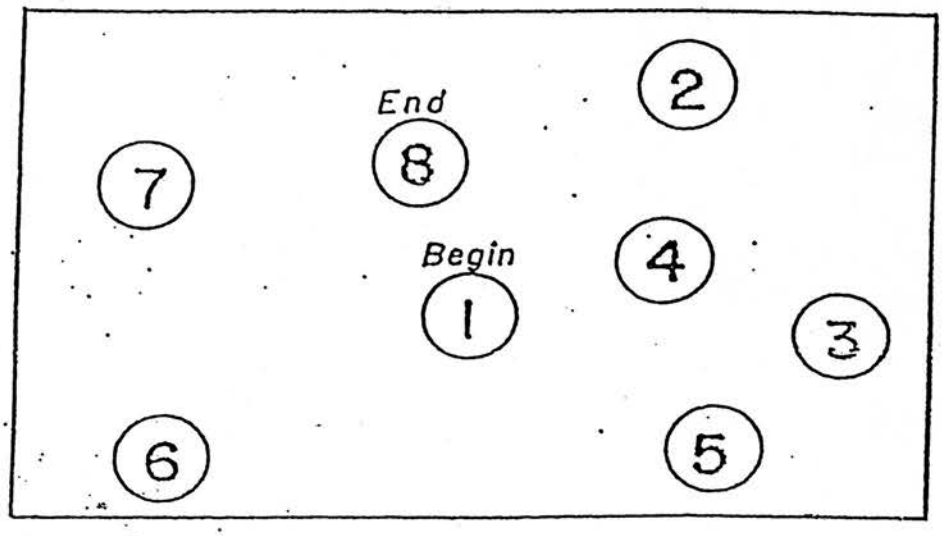
Scaled score •

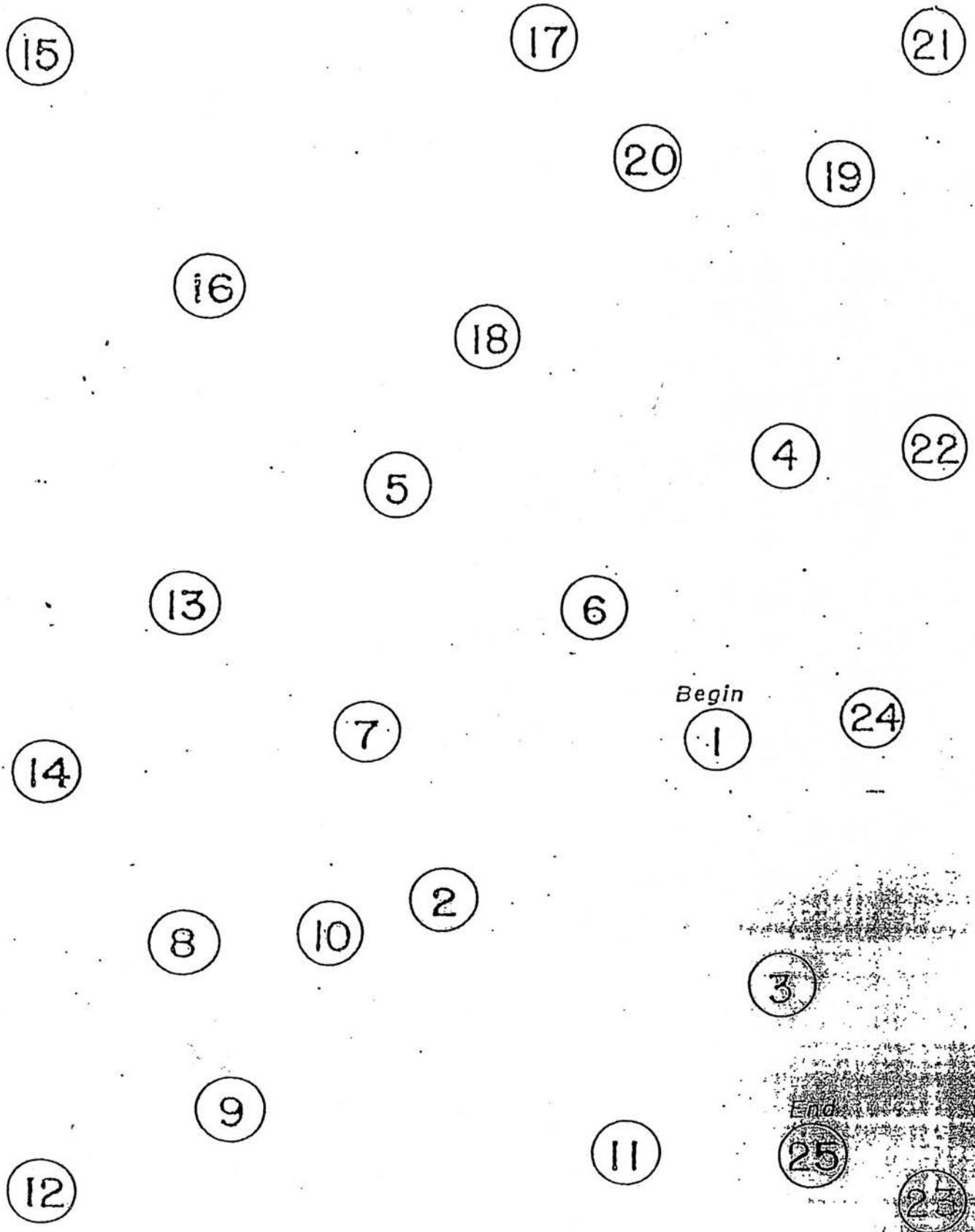
Table D		
Raw score	Scaled score	Classification
0–7	10	Very superior
8	9	Superior
9–10	8	Good
11–13	7	High average
14–17	6	Average
18–20	5	Moderate ave.
21–23	4	Low average
24–25	3	Poor
26–31	2	Abnormal
> 31	1	Impaired

TEST V: TRAIL MAKING

Part A

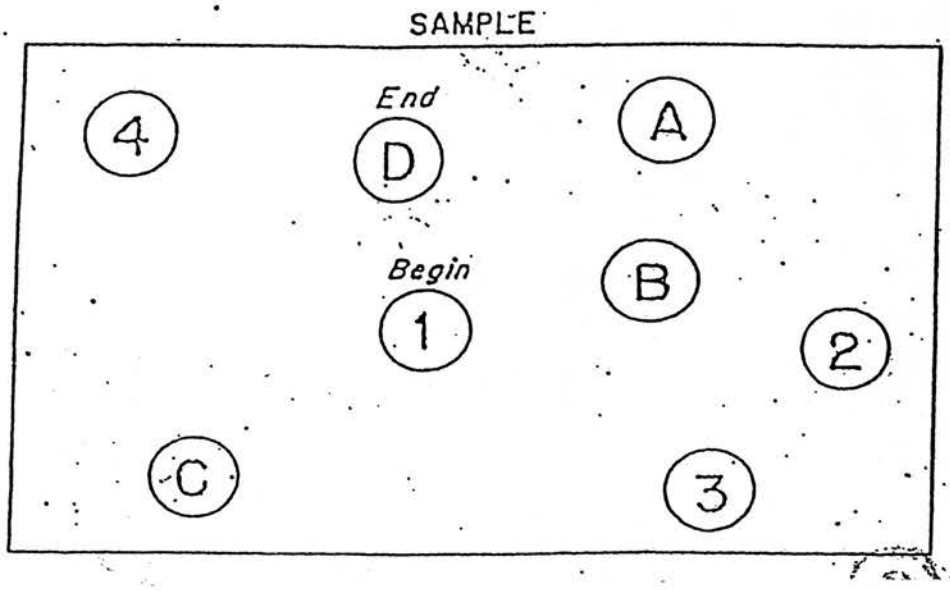
SAMPLE

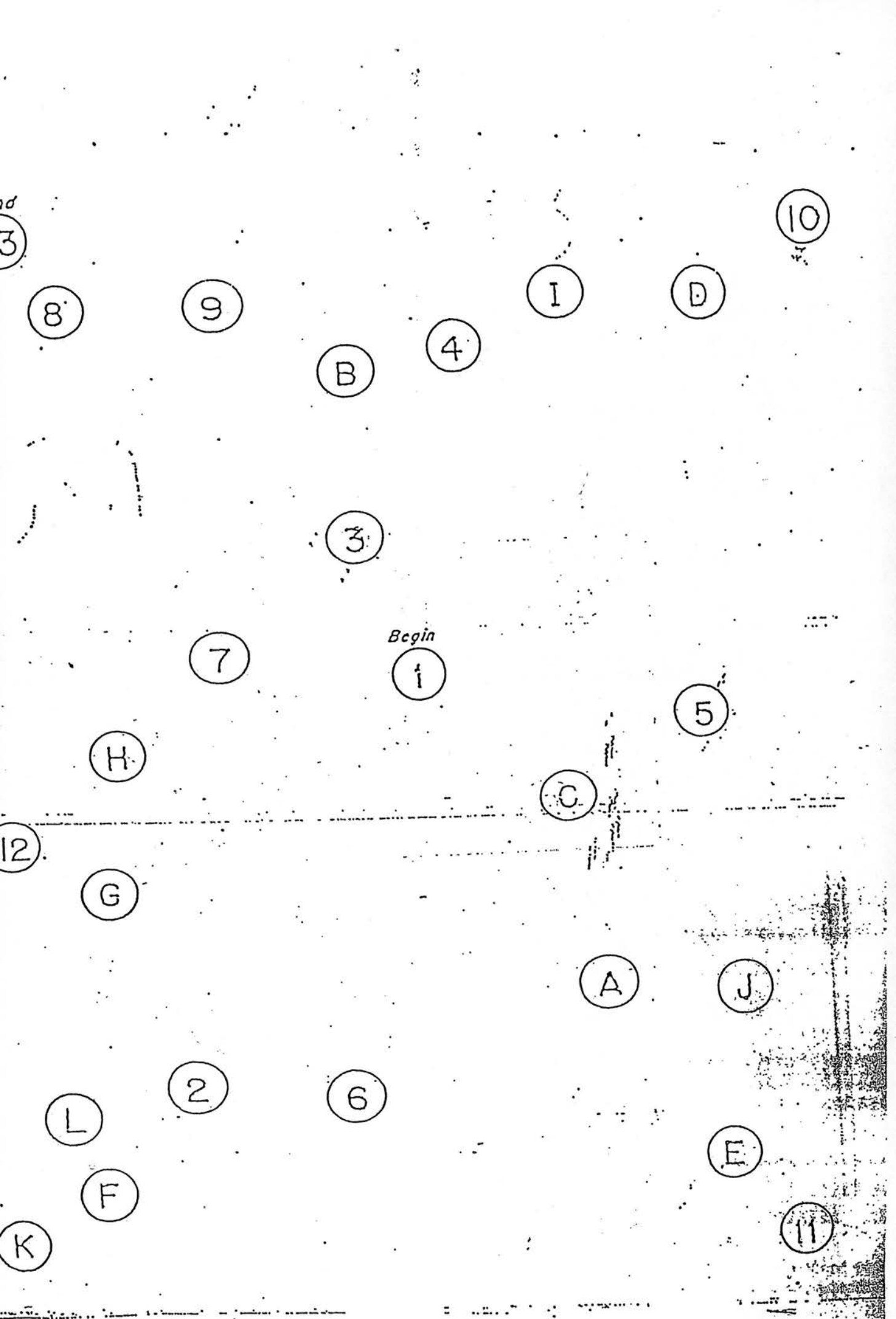



15
17
21
20
19
16
18
4
22
5
13
6
Begin
1
24
7
14
2
8
10
3
9
End
11
25
12

TEST V: TRAIL MAKING

Part B




10
I
D
8
9
4
B
3
Begin
7
1
5
H
C
12
G
A
J
2
6
L
E
F
11
K

Form C Stimulus Sheet

BLUE	RED	TAN	RED
GREEN	GREEN	RED	TAN
TAN	TAN	TAN	RED
RED	BLUE	BLUE	TAN
GREEN	GREEN	TAN	BLUE
BLUE	BLUE	RED	GREEN
GREEN	TAN	GREEN	RED
BLUE	GREEN	RED	BLUE
RED	TAN	BLUE	RED
BLUE	BLUE	TAN	TAN
TAN	GREEN	RED	GREEN
RED	BLUE	GREEN	TAN
TAN	GREEN	RED	BLUE
GREEN	RED	TAN	RED
BLUE	BLUE	BLUE	BLUE
TAN	GREEN	TAN	RED
GREEN	TAN	GREEN	GREEN
RED	RED	TAN	RED
TAN	TAN	BLUE	BLUE
RED	GREEN	TAN	TAN
TAN	TAN	BLUE	BLUE
RED	RED	GREEN	GREEN
GREEN	BLUE	RED	BLUE
RED	RED	GREEN	RED
TAN	GREEN	TAN	BLUE
BLUE	RED	RED	TAN
GREEN	TAN	GREEN	BLUE
TAN	BLUE	BLUE	GREEN

Form C Responses–Color Task

1 BLUE_____	29 RED_____	57 TAN_____	85 RED_____
2 GREEN_____	30 GREEN_____	58 RED_____	86 TAN_____
3 TAN_____	31 TAN_____	59 TAN_____	87 RED_____
4 RED_____	32 BLUE_____	60 BLUE_____	88 TAN_____
5 GREEN_____	33 GREEN_____	61 TAN_____	89 BLUE_____
6 BLUE_____	34 BLUE_____	62 RED_____	90 GREEN_____
7 GREEN_____	35 TAN_____	63 GREEN_____	91 RED_____
8 BLUE_____	36 GREEN_____	64 RED_____	92 BLUE_____
9 RED_____	37 TAN_____	65 BLUE_____	93 RED_____
10 BLUE_____	38 BLUE_____	66 TAN_____	94 TAN_____
11 TAN_____	39 GREEN_____	67 RED_____	95 GREEN_____
12 RED_____	40 BLUE_____	68 GREEN_____	96 TAN_____
13 TAN_____	41 GREEN_____	69 RED_____	97 BLUE_____
14 GREEN_____	42 RED_____	70 TAN_____	98 RED_____
15 BLUE_____	43 BLUE_____	71 BLUE_____	99 BLUE_____
16 TAN_____	44 GREEN_____	72 TAN_____	100 RED_____
17 GREEN_____	45 TAN_____	73 GREEN_____	101 GREEN_____
18 RED_____	46 RED_____	74 TAN_____	102 RED_____
19 TAN_____	47 TAN_____	75 BLUE_____	103 BLUE_____
20 RED_____	48 GREEN_____	76 TAN_____	104 TAN_____
21 TAN_____	49 TAN_____	77 BLUE_____	105 BLUE_____
22 RED_____	50 RED_____	78 GREEN_____	106 GREEN_____
23 GREEN_____	51 BLUE_____	79 RED_____	107 BLUE_____
24 RED_____	52 RED_____	80 GREEN_____	108 RED_____
25 TAN_____	53 GREEN_____	81 TAN_____	109 BLUE_____
26 BLUE_____	54 RED_____	82 RED_____	110 TAN_____
27 GREEN_____	55 TAN_____	83 GREEN_____	111 BLUE_____
28 TAN_____	56 BLUE_____	84 BLUE_____	112 GREEN_____

Form C-W Stimulus Sheet

BLUE	GREEN	RED	GREEN
GREEN	BLUE	GREEN	TAN
RED	RED	BLUE	RED
TAN	BLUE	TAN	TAN
GREEN	TAN	RED	BLUE
BLUE	RED	TAN	TAN
RED	GREEN	BLUE	GREEN
TAN	TAN	TAN	RED
RED	GREEN	RED	GREEN
BLUE	BLUE	BLUE	RED
RED	RED	RED	BLUE
TAN	TAN	TAN	GREEN
BLUE	GREEN	BLUE	TAN
TAN	RED	GREEN	BLUE
RED	BLUE	TAN	GREEN
BLUE	GREEN	BLUE	RED
GREEN	RED	TAN	GREEN
TAN	GREEN	BLUE	TAN
GREEN	BLUE	RED	GREEN
TAN	TAN	GREEN	BLUE
RED	GREEN	BLUE	TAN
BLUE	RED	GREEN	BLUE
RED	TAN	BLUE	GREEN
TAN	BLUE	GREEN	RED
RED	TAN	RED	BLUE
TAN	RED	GREEN	GREEN
GREEN	TAN	TAN	RED
TAN	GREEN	RED	BLUE

Publications arising from this work

Smith, D.J., Muir, W.J., Blackwood, D.H.R. (2005) Neurocognitive impairment in euthymic young adults with recurrent major depressive disorder and bipolar spectrum disorder. *Bipolar Disorders*, in press.

Smith, D.J., Harrison, N., Muir, W., Blackwood, D.H.R. (2005) The high prevalence of bipolar spectrum disorders in young adults with recurrent depression: towards an innovative diagnostic framework. *Journal of Affective Disorders*, 84 (2-3), 167-178.

Smith, D.J. and Blackwood, D.H.R. (2004) Depression in young adults. *Advances in Psychiatric Treatment*, 10, 4-12.